FACULTY OF PHYSICAL EDUCATION AND SPORT UK

The Analysis of the Effect of HBOT in Patients After Acute Ischemic Stroke

Master's Thesis

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Summary

The purpose of this report is to give an analysis of the effectiveness of HBOT in patients after stroke. This can be achieved by illustrate the main pathophysiologic reactions, including inflammatory a reparatory mechanisms that all brain cells undergo during ischemic brain attack. The fundamentals of stroke where reviewed with the aim of achieving a clear view on the subject. Hence the recognition of therapeutic specificity that hyperbaric oxygen therapy (HBOT) offers. We also took a closer look on the basics of HBO, its history, physiological aspects, indications, the principles that accompany it. An analysis of methods, results, and conclusions of a literature review on the use of this therapy (HBOT) to treat manifestations of stroke in humans is assessed.

Key words: Hyperoxygenation, adjuvant therapy, HBOT, therapeutic hyperbaric medicine, Acute Ischemic stroke, Neuronal cells, Non-neuronal cells.

DEDICATION:

I dedicate this work to Meme (W.Jason) Tate (J.Jason)
To my brother Gerald, Sisters Nelago, Pamwenase, Oye ombiliyetu and my two nieces Pelagia and Babra, To Jana, my guidian angel
And to Wunnie Brima, my other half. What a wonderful adventure we're on.

ACKNOWLEDGEMENTS:

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DECLARATION

I declare that, this is my personal work which I elaborated using the literature listed and the knowledge I gained throughout my studies at Charles University, in the department of Physiotherapy.

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Tufikameni Jason

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LIST OF ABBREVIATIONS:

ATA = Atmospheres absolute

ATM = Atmosphere

AMPA= *a*-amino-3-hydroxy-5-methyl-4 isoxazolepropionic acid

CDER = Center for Drug Evaluation and Research

CDRH = Center for Devices and Radiological Health

CINAHL = Cumulative Index to Nursing & Allied Health

CNS = Central nervous system

CT = Computerized tomography

DARE = Database of Abstracts of Reviews of Effectiveness

EEG = Electroencephalogram

FSW = Feet of sea water

EIAB = Extra- intracranial arterial bypass

FIM = Functional Independence Measure

GCS = Glasgow Coma Scale

GMFM = Gross Motor Function Measure

GOS = Glasgow Outcomes Scale

HBOT = Hyperbaric oxygen therapy

HealthSTAR = Health Service Technology, Administration and Research

ICP = Intracranial pressure

ICU = Intensive Care Unit

IND = Investigational New Drug Application

IRB = Institutional Review Board

JCAHO = Joint Commission on Accreditation of Healthcare Organizations

LOS = Length of stay

MANTIS = Manual, Alternative and Natural Therapy

MRI = Magnetic resonance imaging

MTP = Mitochondrial transition pore

NMDA=*N*methyl-D-aspartate

NOS = Nitric oxide synthase

NRCT = Nonrandomized controlled trial

NS = Nonsignificant

PEDI = Pediatric Evaluation of Disabilities Inventory

ROS = reactive oxygen species

RNS = reactive nitrogen species

RCT = Randomized controlled trial

SCUBA = self-contained underwater breathing apparatus

SOD = Superoxide dismutase

SPECT = Single Photon Emission Computed Tomography

TBI = Traumatic brain injury

TEAG = Technical Expert Advisory Group

TIA = Transient ischemic

INTRODUCTION

Hyperbaric Medicine is the use of barometric pressure for delivering increased concentrations of oxygen dissolved in plasma to body tissues. Hyperbaric oxygen therapy (HBO) is a form of treatment in which a patient breathes 100% oxygen at higher than normal atmospheric pressure that is greater than 1 atmosphere absolute (ATA) (Tarun Sahni, S. Hukku, Madhur Jain, Arun Prasad, Rajendra Prasad, Kuldeep Singh, 2004). Therapy is administered in special therapeutic pressurized chambers, which were earlier used primarily to treat illnesses of deep sea divers. In the sixties HBO went out of practice because of its use without adequate scientific validation. Over the last two decades, animal studies, clinical trials and well-validated clinical experience has proved efficiency of HBO in many indications and there is recently a renewed interest in this field all over the world. HBOT has become the definitive therapy for patients with decompression illness, gas embolism, and severe, acute carbon monoxide poisoning and is a widely accepted treatment for osteoradionecrosis, soft tissue radionecrosis (McDonagh M, september 2003), acute traumatic wounds, Crush injuries, Burns, Gas gangrene and compartment syndrome are indications where addition of Hyperbaric oxygen may be life and limb saving. Patients who have been suffering with non healing ulcers, Decubitus Ulcers (Bed sores) and all late sequelae of Radiation therapy are also benefited with HBO therapy. Acute hearing loss and many neurological illnesses are also now known to possibly benefit from Hyperbaric Oxygen Therapy. With continuing growth all over the world Hyperbaric Medicine has found a distinct role in the modern era of evidence-based medicine (Tarun Sahni, S. Hukku, Madhur Jain, Arun Prasad, Rajendra Prasad, Kuldeep Singh, 2004).

WHO defines stroke as a rapid development of clinical signs of cerebral dysfunction with signs lasting ≥ 24 hrs or leading to death with no apparent cause other than that of vascular origin. Stroke is also referred to as a sudden interruption of the blood supply to the brain, usually caused by a blocked artery or a ruptured blood vessel, leading to an interruption of homeostasis of cells, and symptoms such as loss of speech and loss of motor function (McDonagh M, september 2003). This condition represents a broad spectrum, from barely perceptible or mild disabilities to devastating ones which are characterized by acute and chronic phases and by changes over time in the type and degree of disability (McDonagh M, september 2003). The use of various diagnostic and therapeutic interventions including pre-hospital intubation, intracranial pressure monitoring, intracranial pressure-directed therapy, and head computed tomography scan utilization vary considerably among different centers. Such variation often signifies a lack of consensus on clinical effectiveness (Abbott, 1972).

The purpose of this report is to give an analysis of the effectiveness of HBOT in patients after stroke. This can be achieved by illustrate the main pathophysiologic reactions, including inflammatory a reparatory mechanisms that all brain cells undergo during ischemic brain attack. The fundamentals of stroke where reviewed with the aim of achieving a clear view on the subject. Hence the recognition of therapeutic specificity that hyperbaric oxygen therapy (HBOT) offers. We also took a closer look on the basics of HBO, its history, physiological aspects, indications, the principles that accompany it. An analysis of methods, results, and conclusions of a literature review on the use of this therapy (HBOT) to treat manifestations of stroke in humans is assessed.

FUNDAMENTALS OF ACUTE ISCHEMIC STROKE

BASIC PATHOPHYSIOLOGY

Since the late 1980s, basic science research in the field of stroke has elucidated multiple pathways of cellular injury and repair after cerebral ischemia, resulting in the identification of several promising targets for neuroprotection. A large number of neuroprotective agents have been shown to reduce stoke-related damage in animal models. To date, however, no single agent has achieved success in clinical trials. Nevertheless, analysis of the reasons behind the failure of recent drug trials, combined with the success of clotlysing drugs in improving clinical outcome, has revealed new potential therapeutic opportunities and raised expectations that successful stroke treatment will be achieved in the near future (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006).

MECHANISMS OF ISCHEMIC CELL DEATH

Ischemic stroke compromises blood flow and energy supply to the brain, which triggers at least five fundamental mechanisms that lead to cell death: excitotoxicity and ionic imbalance, oxidative/nitrative stress, inflammation,

apoptosis, and peri-infarct depolarization (Fig. 1) (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006).

These pathophysiological processes evolve in a series of complex spatial and temporal events spread out over hours or even days (Fig.2), have overlapping and redundant features, and mediate injury within neurons, glial cells, and vascular elements (Barone FC, Feuerstein GZ , 1999).

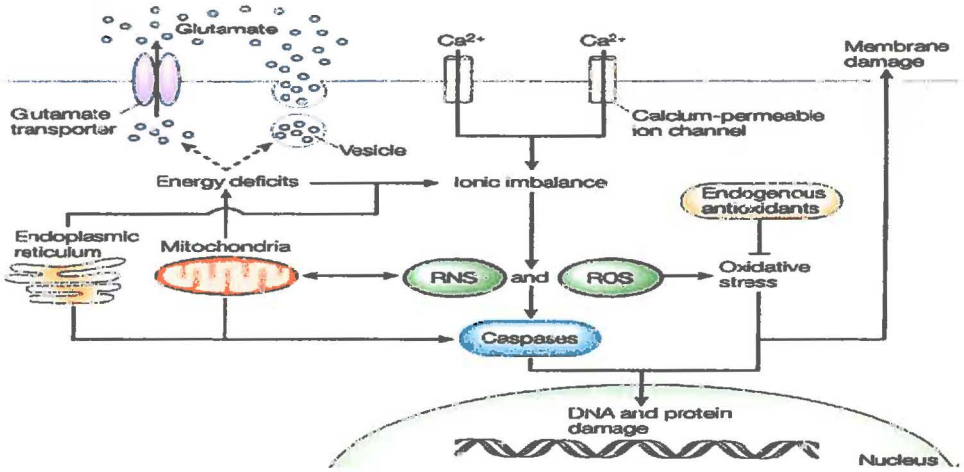


FIGURE 1 Major Pathways Implicated In Ischemic Cell Death

Excitotoxicity, ionic imbalance, oxidative and nitrative stresses, and apoptotic-like mechanisms. There is extensive interaction and overlap between multiple mediators of cell injury and cell death. After ischemic onset, loss of energy substrates leads to mitochondrial dysfunction and the generation of reactive oxygen species (*ROS*) and reactive nitrogen species (*RNS*). Additionally, energy deficits lead to ionic imbalance and excitotoxic glutamate efflux and build up of intracellular calcium. Downstream pathways ultimately include direct free radical damage to membrane lipids, cellular proteins, and DNA, as well as calcium-activated proteases, plus caspase cascades that dismantle a wide range of homeostatic, reparative, and cytoskeletal proteins. (Lo EH, Dalkara T, Moskowitz MA, 2003)

Figure 2 graphically shows the relative contribution of each process to the net stroke-related injury. Within areas of severely reduced blood flow – the "core" of the ischemic territory – excitotoxic and necrotic cell death occurs within minutes, and tissue undergoes irreversible damage in the absence of prompt and adequate reperfusion. However, cells in the peripheral zones are supported by collateral circulation, and their fate is determined by several factors including the degree of ischemia and timing of reperfusion. In this

peripheral region, termed the "ischemic penumbra," cell death occurs relatively slowly via the active cell death mechanisms noted above; targeting these mechanisms provides promising therapeutic opportunities. (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006)

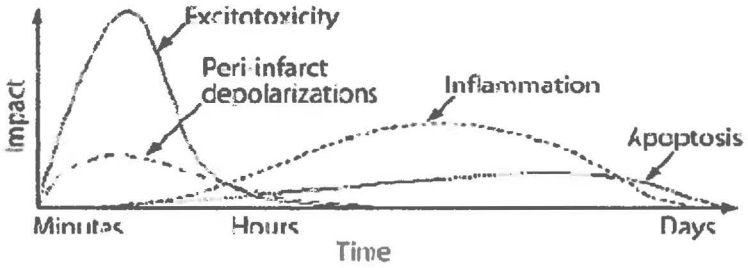


FIGURE 2 Putative Cascade of Damaging Events in the Focal Cerebral Ischemia

Very early after the onset of the focal perfusion deficit, excitotoxic mechanisms can damage neurons and glia lethally. In addition, excitotoxicity triggers a number of events that can further contribute to the demise of the tissue. Such events include peri-infarct depolarizations and the more-delayed mechanisms of inflammation and programmed cell death. The *x*-axis reflects the evolution of the cascade over time, while the *y*-axis aims to illustrate the impact of each element of the cascade on the final outcome. (From Dirnagel et al., *Trends Neurosci* 1999; 22: 391–397)

EXCITOTOXICITY AND IONIC IMBALANCE

Ischemic stroke results in impaired cellular energy metabolism and failure of energy-dependent processes such as the sodium-potassium ATPase. Loss of energy stores results in ionic imbalance, neurotransmitter release, and inhibition of the reuptake of excitatory neurotransmitters such as glutamate. Glutamate binding to ionotropic *N*methyl-D-aspartate (NMDA) and *a*-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors promotes excessive calcium influx that triggers a wide array of downstream

phospholipases and proteases, which in turn degrade membranes and proteins essential for cellular integrity (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006). Experimental models of stroke, indicates extracellular glutamate levels increase in the microdialysate, and glutamate receptor blockade attenuates stroke lesion volumes (Shimizu-Sasamata M, Bosque-Hamilton P, Huang PL, Moskowitz MA,Lo EH, 1998) (Wang X, Shimizu-Sasamata M, Moskowitz MA, Newcomb R, Lo EH, 2001). NMDA receptor antagonists prevent the expansion of stroke lesions in part by blocking spontaneous and spreading depolarization of neurons and glia (cortical spreading depression) (Hossmann.KA, 1996). Recent studies noted that activation of the metabotropic subfamily of receptors has been implicated in glutamate excitotoxicity (Bruno V, Battaglia G, Copani A, D'Onofrio M, Di Iorio P, De Blasi A, Melchiorri D, Flor PJ, Nicoletti F , 2001). Up - and down regulation of specific glutamate receptor subunits contribute to stroke pathophysiology in different ways (Michaelis.EK, 1998). For instance, after global cerebral ischemia, there is a relative reduction of calcium impermeable GluR2 subunits in AMPA-type receptors, making these receptors more permeable to deleterious calcium influx (Pellegrini-Giampietro DE, Zukin RS, Bennett MV, Cho S, Pulsinelli WA , 1992). Antisense knock down of calcium-impermeable GluR2 subunits significantly increased hippocampal injury in a rat model of transient global cerebral ischemia, confirming the importance of these regulatory subunits in mediating neuronal vulnerability (Oguro K, Oguro N, Kojima T, Grooms SY, Calderone A,Zheng X, Bennett MV, Zukin RS , 1999). Depending upon the subtype, metabotropic glutamate receptors can trigger either pro-survival or pro-death signals in ischemic neurons (Bruno V, Battaglia G, Copani A, D'Onofrio M, Di Iorio P, De Blasi A, Melchiorri D, Flor PJ, Nicoletti F , 2001). Understanding how the expression of specific glutamate receptor subunits modifies cell survival should stimulate the search for stroke neuroprotective drugs that selectively target specific subunits. Ionotropic

glutamate receptors also promote perturbations in ionic homeostasis that play a critical role in cerebral ischemia (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006). For example, L-, P/Q-, and N-type calcium channel receptors mediate excessive calcium influx, and calcium channel antagonists reduce ischemic brain injury in preclinical studies (Horn J, Limburg M , 2001) (Zipfel GJ, Lee JM, Choi DW , 1999). Zinc is stored in vesicles of excitatory neurons and co-released upon depolarization after focal cerebral ischemia, resulting in neuronal death (Weiss JH, Hartley DM, Koh JY, Choi DW , 1993) (Sorensen JC, Mattsson B, Andreasen A, Johansson BB , 1998). Recently, imbalances in potassium have also been implicated in ischemic cell death (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006). Compounds that selectively modulate a class of calcium sensitive high conductance potassium (maxi-K) channels protect the brain against stroke in animal models (Gribkoff VK, Starrett JE Jr., Dworetzky SI, Hewawasam P, Boissard CG, Cook DA, Frantz SW, Heman K, Hibbard JR, Huston K, Johnson G, Krishnan BS, Kinney GG, Lombardo LA,Meanwell NA,Molinoff PB,Myers RA,Moon SL, Ortiz A, Pajor L, Pieschl RL, Post-Munson DJ,, 2001).

OXIDATIVE AND NITRATIVE STRESS

Reactive oxygen species (ROS) such as superoxide and hydroxyl radicals are known to mediate reperfusion-related tissue damage in several organ systems including the brain, heart, and kidneys (Chan, 2001). Oxygen free radicals are normally produced by the mitochondria during electron transport, and, after ischemia, high levels of intracellular Ca2+, Na+, and ADP stimulate excessive mitochondrial oxygen radical production. Oxygen

radical production may be especially harmful to the injured brain because levels of endogenous antioxidant enzymes [including superoxide dismutase (SOD), catalase, glutathione], and antioxidant vitamins (e.g., alpha-tocopherol, and ascorbic acid) are normally not high enough to match excess radical formation. After ischemia reperfusion, enhanced production of ROS overwhelms endogenous scavenging mechanisms and directly damages lipids, proteins, nucleic acids, and carbohydrates (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006). Importantly, oxygen radicals and oxidative stress facilitate mitochondrial transition pore (MTP) formation, which dissipates the proton motive force required for oxidative phosphorylation and ATP generation (Kroemer G, Reed JC, 2000). As a result, mitochondria release apoptosis-related proteins and other constituents within the inner and outer mitochondrial membranes (Bernardi P, Petronilli V, Di Lisa F, Forte M, 2001). Upon reperfusion and renewed tissue oxygenation, dysfunctional mitochondria may generate oxidative stress and MTP formation. Oxygen radicals are also produced during enzymatic conversions such as the cyclooxygenase-dependent conversion of arachidonic acid to prostanoids and degradation of hypoxanthine, especially upon reperfusion. Furthermore, free radicals are also generated during the inflammatory response after ischemia (see below). Not surprisingly then, oxidative stress, excitotoxicity, energy failure, and ionic imbalances are inextricably linked and contribute to ischemic cell death. Oxidative and nitrative stresses are modulated by enzyme systems such as SOD and the nitric oxide synthase (NOS) family (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006). The important role of SOD in cerebral ischemia is demonstrated in studies showing that mice with enhanced SOD expression show reduced injury after cerebral ischemia whereas those with a deficiency show increased injury (Kinouchi H, Epstein CJ,Mizui T, Carlson E, Chen SF, ChanPH, 1991), (Sheng H, Bart RD,Oury TD,Pearlstein RD,Crapo JD,Warner DS, 1999) (Kim GW, Kondo T, Noshita N, Chan PH, 2002). Similarly, in the case of NOS, stroke-induced injury is

attenuated in mice with deficient expression of the neuronal and inducible NOS isoforms (Huang Z, Huang PL, Panahian N, Dalkara T, Fishman MCMoskowitz MA , 1994), (Iadecola C, Zhang F, Casey R,Nagayama M,Ross ME, 1997). NOS activation during ischemia increases the generation of NO production, which combines with superoxide to produce peroxynitrite, a potent oxidant (Beckman JS, Beckman TW, Chen J, Marshall PA, Freeman BA, 1999). The generation of NO and oxidative stress is also linked to DNA damage and activation of poly(ADP-ribose) polymerase-1 (PARP-1), a nuclear enzyme that facilitates DNA repair and regulates transcription (Zhang J, Dawson VL, Dawson TM, Snyder SH, 1994). PARP-1 catalyzes the transformation of *b*-nicotinamide adenine dinucleotide (NAD+) into nicotinamide and poly (ADP-ribose). In response to DNA strand breaks, PARP-1 activity becomes excessive and depletes the cell of NAD+ and possibly ATP (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006). Inhibiting PARP-1 activity or deleting the *parp-1* gene reduces apoptotic and necrotic cell death (Eliasson MJ, Sampei K,Mandir AS,Hurn PD,Traystman RJ Bao J, Pieper A,Wang ZQ, Dawson TM, Snyder SH, Dawson VL, 1997), (Endres M,Wang ZQ, Namura S,Waeber C,Moskowitz MA, 1997), pointing to the possible relevance of this enzyme as a target for stroke therapy.

APOPTOSIS

Apoptosis, or programmed cell death (Yuan J, Yankner BA , 2000), is characterized histologically by cells positive for terminaldeoxynucleotidyl-transferase-mediated dUTP nick end labeling (TUNEL) that exhibit DNA laddering. Necrotic cells, in contrast, show mitochondrial and nuclear swelling, dissolution of organelles, nuclear chromatin condensation,

followed by rupture of nuclear and cytoplasmic membranes, and the degradation of DNA by random enzymatic cuts. Cell type, cell age, and brain location render cells more or less resistant to apoptosis or necrosis. Mild ischemic injury preferentially induces cell death via an apoptotic-like process rather than necrosis, although "aponecrosis" more accurately describes the pathology. Apoptosis occurs via caspase-dependent as well as caspase-independent mechanisms (Fig. 3). Caspases are protein-cleaving enzymes (zymogens) that belong to a family of cysteine aspartases constitutively expressed in both adult and especially newborn brain cells, particularly neurons (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006).

The mechanisms of cleavage and activation of caspases in human brain are believed to be similar to those documented in experimental models of stroke, trauma, and neurodegeneration (Chopp M, Chan PH, Hsu CY, Cheung ME, Jacobs TP, 1996). Apoptogenic triggers include oxygen free radicals, Bcl2, death receptor ligation, DNA damage, and possibly lysosomal protease activation (Nicotera P, Lipton SA, 1999), (Budd SL, Tenneti L, Lishnak T, Lipton SA, 2000), (Martin-Villalba A, Herr I, Jeremias I, Hahne M, Brandt R Vogel J, Schenkel J, Herdegen T, Debatin KM, 1999),(GS, 2001).

Since caspase-dependent cell death requires energy in the form of ATP, apoptosis predominantly occurs in the ischemic penumbra (which sustains milder injury) rather than in the ischemic core, where ATP levels are rapidly depleted (Nicotera P, Leist M, Fava E, Berliocchi L,Volbracht C, 2000). Microglial cells become activated in these areas, this may be either as a sign of neuronal deafferentation or of neuronophagia (Pappata, S., Levasseur, M.m Gunn, R.N.,Myers, R., Crouzel, C.,Syrota, A.,Jones, T., Kreutzberg, G.W., and Banati, R.B. , 2000). Glial cells may be involved in stroke-induced apoptosis in several ways:

- By producing signals that induce apoptosis in neurons

- By dying apoptotically triggered by the same signals and in a manner similar to that of neurons (in particular oligodendrocytes: Mabuchi et al., 2000)
- By self-elimination via apoptosis
- By producing factors that protect neurons against apoptosis

All these processes are closely connected with inflammation. Inflammation produces toxins like oxygen free radicals that induce mitochondrial and DNA damage as important upstream mediators of apoptosis in neurons and oligodendrocytes. In addition, apoptosis is a critical mechanism in limiting and terminating inflammation, although it is controversial whether inflammatory cells themselves are eliminated by apoptosis Dirnagle et al. It is very likely that astrocytes play a major role in limiting the growth of ischemic lesions, and that antiapoptotic mechanisms are a key element to astrocyte-mediated neuroprotection after stroke. Astrocytes are a major source of growth factors that protect neurons against ischemic damage. Reactive astrocytes are a major source of growth factors that protect neurons against ischemic damage. Reactive astrocytes produce nerve growth factor, basic fibroblast growth factor, brain-derived nerve growth factor, ciliary neurotrophic factor, insulin-like growth factor-1 among others. (W.J.Koroshetz, R.G.González, 2006)

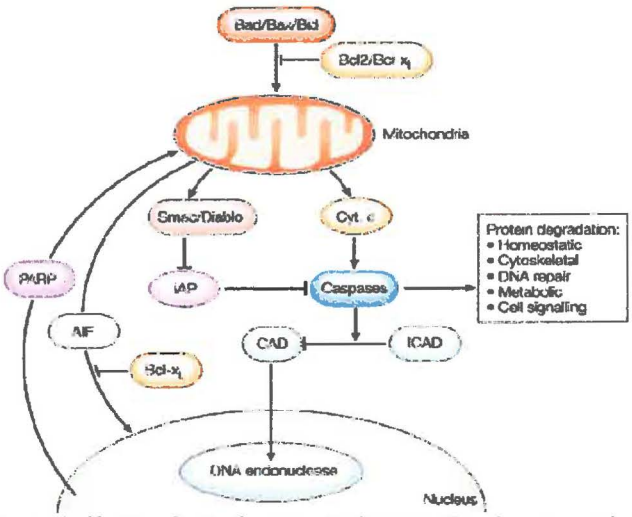


FIGURE 3 Cell Death Pathways Relevant To An Apoptic-Like Mechanism In Cerebral Ischemia:

Release of cytochrome *c* (*Cyt.c*) from the mitochondria is modulated by pro- as well as anti-apoptotic Bcl2 family members. Cytochrome *c* release activates downstream caspases through apoptosome formation (not shown) and caspase activation can be modulated by secondary mitochondria-derived activator of caspase (*Smac/Diablo*) indirectly through suppressing protein inhibitors of apoptosis (*IAP*). Effector caspases (caspases 3 and 7) target several substrates, which dismantle the cell by cleaving homeostatic, cytoskeletal, repair, metabolic, and cell signaling proteins.Caspases also activate caspase-activated deoxyribonuclease (*CAD*) by cleavage of an inhibitor protein (*ICAD*). Caspase-independent cell death may also be important. One mechanism proposes that poly-ADP (ribose) polymerase activation (*PARP*) promotes the release of apoptosis-inducing factor (*AIF*), which translocates to the nucleus, binds to DNA, and promotes cell death through a mechanism that awaits clarification. (From Lo et al., *Nat Rev Neurosci* 2003, 4: 399–415)

INFLAMMATION

Inflammation is intricately related to the onset of stroke, and to subsequent stroke-related tissue damage. Inflammation within the arterial wall plays a vital role in promoting atherosclerosis (Elkind MS, Cheng J, Boden-Albala B, Rundek T, Thomas J,Chen H, Rabbani LE, Sacco RL , 2002). Arterial thrombosis (usually associated with ulcerated plaques) is triggered by multiple processes involving endothelial activation, as well as pro-inflammatory and pro-thrombotic interactions between the vessel wall and circulating blood elements (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006).

Ischemic stroke-related brain injury itself triggers inflammatory cascades within the parenchyma that further amplify tissue damage (Barone FC), (del Zoppo G, Ginis I, Hallenbeck JM, Iadecola C,Wang X,Feuerstein GZ , 2000). As reactive microglia, macrophages, and leukocytes are recruited into ischemic brain, inflammatory mediators are generated by these cells as well as by neurons and astrocytes (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006). Inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), interleukin-1 (IL-1), and monocyte chemoat tractant protein-1 (MCP-1) are key inflammatory mediators, as evidenced by attenuated ischemic injury in mutant mice with targeted

disruption of their genes (Hughes PM, Allegrini PR, Rudin M, Perry VH, Mir AK, Wiessner C , 2002), (Boutin H,LeFeuvre RA,Horai R,Asano M, Iwakura Y,Rothwell NJ, 2001). Initially after occlusion, there is a transient up regulation of immediate early genes encoding transcription factors (e.g., c-*fos*, c-*jun*) that occurs within minutes. This is followed by a second wave of heat shock genes (e.g., *HSP70*, *HSP72*) that increase within 1–2 h and then decrease by 1–2 days. Approximately 12–24 h after a stroke, a third wave comprised of chemokines and cytokines is expressed (e.g., IL-1, IL-6, IL-8, TNF-*a*, MCP-1, etc.). It is not known whether these three waves are causally related. Inflammatory cascades stimulate both detrimental and potentially beneficial pathways after ischemia (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006). Similarly, the peptide vascular endothelial growth factor (VEGF) exacerbates edema in the acute phase of cerebral ischemia but promotes vascular remodeling during stroke recovery (Zhang ZG, Zhang L, Jiang Q, Zhang R, Davies K, Powers C, Bruggen N, Chopp M, 2000). Ultimately, the net effect of these mediators depends upon the stage of tissue injury or the predominance of a single signaling cascade among multiple divergent pathways (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006).

PERI-INFARCT DEPOLARIZATIONS

Brain tissue depolarizations after ischemic stroke are believed to play a vital role in recruiting adjacent penumbral regions of reversible injury into the core area of infarction. Cortical spreading depression (CSD) is a self-propagating wave of electrochemical activity that advances through neural tissues at a rate of 2–5 mm/min, causing prolonged (1–5 min) cellular depolarization, depressed neuro-electrical activity, potassium and glutamate

release into adjacent tissue and reversible loss of membrane ionic gradients (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006). CSD is associated with a change in the levels of numerous factors including immediate early genes, growth factors, and inflammatory mediators such as interleukin- 1*b* and TNF-*a* (Jander S, Schroeter M, Peters O,Witte OW, Stoll G , 2001). CSD is a reversible phenomenon, and, while implicated in conditions such as migraine, reportedly does not cause permanent tissue injury in humans (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006). In severely ischemic regions, energy failure is so profound that ionic disturbances and simultaneous depolarizations become permanent, a process termed anoxic depolarization (Hansen AJ,Nedergaard M , 1988). In penumbral regions after stroke, where blood supply is compromised, spreading depression exacerbates tissue damage, perhaps due to the increased energy requirements for reestablishing ionic equilibrium in the metabolically compromised ischemic tissues (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006). In this context, spreading depression waves are referred to as peri-infarct depolarizations (PIDs), reflecting their pathogenic role and similarity to anoxic depolarization (Hossmann.KA, 1996). PIDs have been demonstrated in mice rat, and cat stroke models (Strong AJ, Smith SE,Whittington DJ,Meldrum BS, Parsons AA,Krupinski J,Hunter AJ,Patel S,Robertson C , 2000), (Gill R, Andine P, Hillered L, Persson L, Hagberg H, 1992); however, their relevance to human stroke pathophysiology remains unclear (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006). In the initial 2–6 h after experimental stroke, PIDs result in a step-wise increase in the region of core-infarcted tissue into adjacent penumbral regions and the incidence and total duration of spreading depression is shown to correlate with infarct size (Iijima T, Mies G, Hossmann KA , 1992), (Busch E, Gyngell ML, Eis M, Hoehn-Berlage M, Hossmann KA, 1996), (Dijkhuizen RM, Beekwilder JP, van der Worp HB, Berkelbach van der Sprenkel JW, Tulleken KA, Nicolay K , (1999). Recent

evidence suggests that PIDs contribute to the expansion of the infarct core throughout the period of infarct maturation (Hartings JA, Rolli ML, Lu XC, Tortella FC , 2003). Inhibition of spreading depression using pharmaceutical agents such as NMDA or glycine antagonists or physiological approaches such as hypothermia, may be an important strategy to suppress the expansion of an ischemic lesion (Hartings JA, Rolli ML, Lu XC, Tortella FC , 2003), (Tatlisumak T, Takano K, Meiler MR, Fisher M , 1998) (Chen Q, Chopp M, Bodzin G, Chen H , 1993).

GREY MATTER VERSUS WHITE MATTER ISCHEMIA

In addition to the size of the stroke, its location, and the relative involvement of gray versus white matter are key determinants of outcome. For example, small white matter strokes often cause extensive neurologic deficits by interrupting the passage of large axonal bundles such as those within the internal capsule. Blood flow in white matter is lower than in gray matter, and white matter ischemia is typically severe, with rapid cell swelling and tissue edema because there is little collateral blood supply in deep white matter. Moreover, cells within the gray and white matter have different susceptibilities to ischemic injury (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006). Amongst the neuronal population, well-defined subsets (the CA1 hippocampal pyramidal neurons, cortical projection neurons in layer 3, neurons in dorsolateral striatum, and cerebellar Purkinje cells) are particularly susceptible and undergo selective death after transient global cerebral ischemia (Petty MA, Wettstein JG , 1999). The major cell types composing the neurovascular module within white matter include the endothelial cell, perinodal astrocyte, axon, oligodendrocyte, and myelin. In general, oligodendrocytes are more vulnerable than astroglial or

endothelial cells (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006). There are important differences in the pathophysiology of white matter ischemia as compared to that of gray matter, which have implications for therapy (PK, 1998). In the case of excitotoxicity, since the white matter lacks synapses, neurotransmitter release from vesicles does not occur despite energy depletion and neurotransmitter accumulation (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006). Instead, there is reversal of Na+ - dependent glutamate transport (Li S, Mealing GA, Morley P, Stys PK , 1999), resulting in glutamate toxicity with subsequent AMPA receptor activation, and excessive accumulation of calcium, which in turn activates calcium-dependent enzymes such as calpain, phospholipases, and protein kinase C, resulting in irreversible injury (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006). The distinct lack of AMPA receptors expressing calcium impermeable GluR2 subunits may make oligodendroglia particularly vulnerable to excitotoxic injury (McDonald JW, Althomsons SP, Hyrc KL, Choi DW, Goldberg MP, 1998). In the case of oxidative stress-induced white matter injury, the severity of injury appears to be greater in large axons as compared to small axons although the mechanisms underlying these differences need further study (Petty MA, Wettstein JG , 1999). Despite these differences between gray and white matter injury, several common cascades of injury do exist (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006). Damaged oligodendrocytes express death signals such as TNF and Fas ligand, and recruit caspase-mediated apoptotic-like pathways (Gu C, Casaccia-Bonnefil P, Srinivasan A, Chao MV , 1999). Degradation of myelin basic protein by matrix metalloproteinases (MMPs), and upregulation of MMPs in autopsied samples from patients with vascular dementia suggest that proteolytic pathways are also recruited in white matter. These pathways might serve as common targets for stroke therapy (Chandler S, Coates R,

Gearing A, Lury J,Wells G, Bone E, 1995) (Rosenberg GA, Sullivan N, Esiri MM , 2001).

THE NEUROVASCULAR UNIT

Neurovascular unit is a modular concept that emphasises the dynamics of vascular, cellular, and matrix signaling in the maintainance of the integrity of brain tissue within both the gray and white matter, and its importance to the pathophysiology of conditions such as stroke, vascular dementia, migraine, trauma, multiple sclerosis, and possibly the aging brain (Fig. 4) (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006). The neurovascular unit places stroke in the context of an integrative tissue response in which all cellular and matrix elements, not just neurons or blood vessels, are players in the evolution of tissue injury (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006). For instance, efficacy of the blood–brain barrier is critically dependent upon endothelial–astrocyte– matrix interactions (Petty MA, Lo EH , 2002).

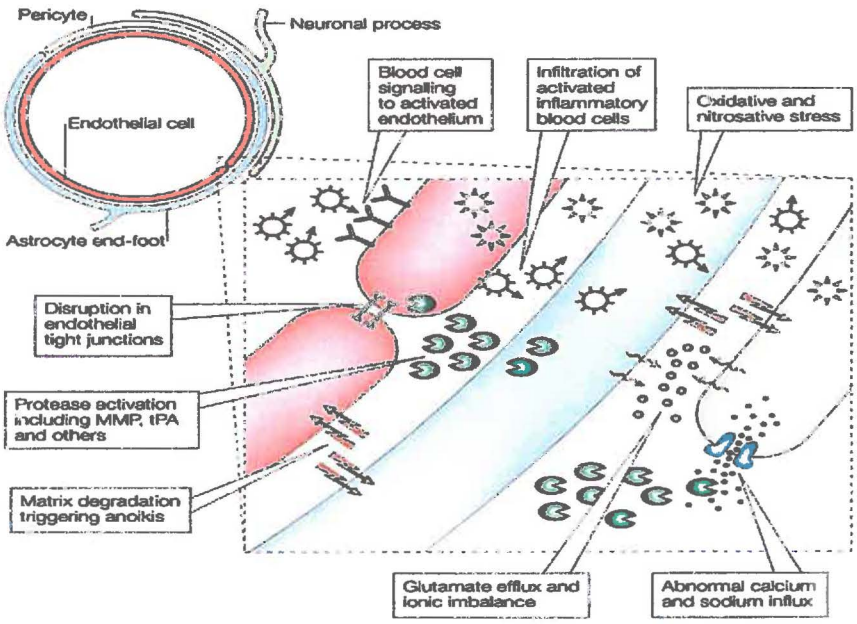


FIGURE 4 Schematic View Of The Neurovascular Unit Or Module And Some Of Its Components:

Circulating blood elements, endothelial cells, astrocytes, extracellular matrix, basal lamina, adjacent neurons, and pericytes. After ischemia, perturbations in neurovascular functional integrity initiate multiple cascades of injury. Upstream signals such as oxidative stress together with neutrophil and/or platelet interactions with activated endothelium upregulate matrix metalloproteinases (*MMPs*), plasminogen activators and other proteases which degrade matrix and lead to blood–brain barrier leakage. Inflammatory infiltrates through the damaged blood–brain barrier amplify brain tissue injury. Additionally, disruption of cell matrix homeostasis may also trigger anoikis-like cell death in both vascular and parenchymal compartments. Overlaps with excitotoxicity have also been documented via t-PA-mediated interactions with the NMDA receptor that augment ionic imbalance and cell death. (*t-PA* Tissue plasminogen activator) (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006).

Disruption of the neurovascular matrix, which includes basement membrane components such as type IV collagen, heparan sulfate proteoglycan, laminin, and fibronectin, upsets the cell–matrix and cell–cell signaling that maintains neurovascular homeostasis. Although many proteases including cathepsins and heparanases contribute to extracellular matrix proteolysis, in the context of stroke, plasminogen activator (PA) and MMP are probably the two most important. This is because tissue plasminogen activator (t-PA) has been used successfully as a stroke therapy, and because emerging data show important linkages between t-PA, MMPs, edema, and hemorrhage after stroke (Aneesh

B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006). The MMPs are zinc endopeptidases produced by all cell types of the neurovascular unit (Yong VW, Krekoski CA, Forsyth PA, Bell R, Edwards DR, 1998), that are secreted as zymogens requiring cleavage for enzymatic activation. MMPs can be classified into:

- gelatinases (MMP-2 and -9),
- collagenases (MMP-1, -8, -13),
- stromelysins (MMP-3, -10, -11),
- membrane-type MMPs (MMP-14, -15, -16, -17), and others (e.g., MMP-7 and -12) (Cuzner ML, Opdenakker G , 1999).

Together with the PA system, MMPs play a central role in brain development and plasticity as they modulate extracellular matrix to allow neurite out growth and cell migration (Yong VW, Power C, Forsyth P, Edwards DR, 2001). Upstream triggers of MMP include MAP kinase pathways and oxidative stress (Wang X,Mori T, Jung JC, Fini ME, Lo EH , 2002), (Gasche Y, Copin JC, Sugawara T, Fujimura M, Chan PH, 2001). MMP signaling is intricately linked to other well-recognized pathways after stroke, including oxidative and nitrative stress, caspase-mediated cell death excitotoxicity, and neuro-inflammation (Gu Z, Kaul M,Yan B, Kridel SJ, Cui J, Strongin A, Smith JW, Liddington RC, Lipton SA, 2002), (Justicia C,Panes J,Sole S,Cervera A,Deulofeu R,Chamorro A, Planas AM , 2003) (Lee SR, Lo EH , 2004).

Several experimental as well as human studies provide evidence for a major role of MMPs (particularly MMP-9) in ischemic stroke, primary brain hemorrhage, blood–brain barrier disruption and post-ischemic or reperfusion hemorrhage (Gasche Y, Fujimura M, Morita-Fujimura Y, Copin JC,Kawase M, Massengale J, Chan PH , 1999),(Asahi M,Asahi K, Jung JC, del Zoppo GJ, Fini ME, Lo EH, 2000) (Montaner J,Alvarez-Sabin J,Molina C,Angles A,AbilleiraS, Arenillas J, Gonzalez MA, Monasterio J, 2001), (Sumii T,Lo EH, 2002), (Abilleira S,Montaner J,Molina CA,Monasterio J, Castillo

J,Alvarez-Sabin J, 2003), (Fukuda S, Fini CA,Mabuchi T,Koziol JA, Eggleston LL Jr., del Zoppo GJ, 2004). Emerging data suggest that administered t-PA upregulates MMP-9 via the low-density lipoprotein receptor-related protein (LRP), which avidly binds t-PA and possesses signaling properties (Wang X,Lee SR,Arai K,Tsuji K,Rebeck GW,Lo EH, 2003). Targeting the t-PA–LRP–MMP pathway may offer new therapeutic approaches for improving the safety profile of t-PA in patients with stroke (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006).

NEUROPROTECTION

Neuroprotection can be defined as the protection of cell bodies and neuronal and glial processes by strategies that impede the development of irreversible ischemic injury by effects on the cellular processes involved. Neuroprotection can be achieved using pharmaceutical or physiological therapies that directly inhibit the biochemical, metabolic, and cellular consequences of ischemic injury, or by using indirect approaches such as t-PA and mechanical devices to restore tissue perfusion (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006). The overlapping complex pathways involving excitotoxicity, ionic imbalance, oxidative and nitrative stress, and apoptotic like mechanisms have been reviewed above. Each of these pathways offers several potential therapeutic targets, several of which have proved successful in reducing ischemic injury in animal models. However, the successful translation of experimental results into clinical practice remains elusive (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006).

CORE AND PENUMBRA

The core generally defined as that part of the ischemic region that is irreversibly injured, while the penumbra is the area of brain that is underperfused and is in danger of infracting. These are useful concepts for several reasons. If they can be identified in the acute ischemic stroke patient they provide prognostic information, and may help guide the patient's management. Importantly, it is now clear that neuroimaging can provide excellent estimates of the core and the penumbra in individual patients (W.J.Koroshetz, R.G.González, 2006).

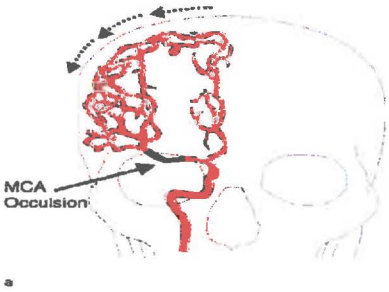


FIGURE 5 ACA Colleteral Flow, FIGURE 6 ACA Collateral Flow after MCA Occlusion

(W.J.Koroshetz, R.G.González, 2006)

To illustrate the core/penumbra concept, let us consider the hypothetical case of an embolus to the main stem portion (M1) of the middle cerebral artery (MCA). The MCA along with the anterior cerebral artery (ACA) arise from the internal carotid artery (ICA) at the base of the frontal lobe (Fig. 5). When an embolus lodges in the M1 segment of the MCA, the MCA territory of the brain becomes underperfused (Fig.6). However, in many cases the collateral circulation from the ACA and posterior cerebral artery can compensate to some degree. The amount of collateral flow determines the size of the core and the penumbra (Figs. 7, 8).

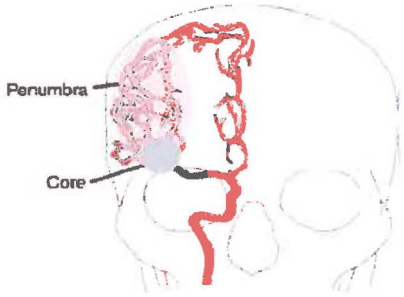
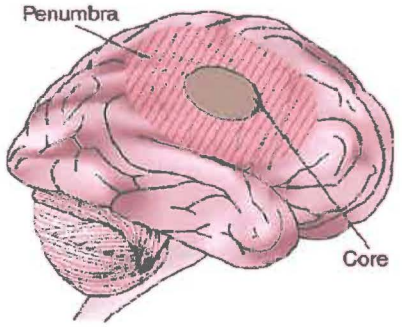


FIGURE 7 Penumbra and Core after MCA Occlusion



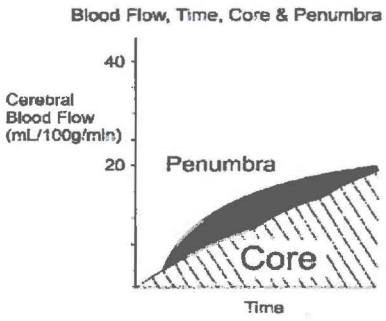


FIGURE 8 Core and Penumbra, FIGURE 9 Blood Flow, Time, Core and Penumbra (W.J.Koroshetz, R.G.González, 2006)

However, it is critical to understand that both the core and penumbra are dynamic entities that depend on the complex physiology that is playing out in the acutely ischemic brain. If the occlusion is not removed, the core size usually increases, while the salvageable penumbra decreases with time (Fig. 9). The rate of change in the size of the core and the penumbra depends on the blood flow provided by the collaterals (W.J.Koroshetz, R.G.González, 2006).

IDENTIFYING THE ISCHEMIC PENUMBRA

While irreversible cell death begins within minutes after stroke onset within regions of maximally reduced blood flow (the infarct "core"), for several hours there exists a surrounding "penumbra" of ischemic but noninfarcted tissue that is potentially salvageable (Hossmann, 1994), (Baron, 2001), (Ginsberg MD, Pulsinelli WA, 1994), (Markus R, Reutens DC, Kazui S, Read S,Wright P, Pearce DC,Tochon-Danguy HJ, Sachinidis JI,Donnan GA, 2004). The concept of an "ischemic penumbra" provides a rationale for the use of neuroprotective drugs and reperfusion techniques to improve outcome after acute ischemic stroke. Then again, the extent of penumbral tissue is thought to diminish rapidly with time, hence the therapeutic time window is narrow (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A. Moskowitz, 2006).

INDUCED HYPERTENSION

The ischemic penumbra shows impaired autoregulation, and appears to be particularly sensitive to blood pressure manipulation. The rationale for using induced hypertension as a stroke therapy is provided by early studies showing that raising mean arterial pressure results in improved cerebral perfusion within the penumbra, and a concomitant return of electrical activity (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006). In animal models of focal cerebral ischemia, induced hypertension therapy was found to augment cerebral blood flow, attenuate brain injury, and improve neurological function (Hayashi S, Nehls DG, Kieck CF, Vielma J, DeGirolami U, Crowell RM, 1984), (Cole DJ,Matsumura JS, Drummond JC, Schell RM , 1992).

HYPEROXIA

Tissue hypoxia plays a critical role in the primary and secondary events leading to cell death after ischemic stroke (Lo EH, Dalkara T, Moskowitz MA , 2003); therefore, increasing brain oxygenation has long been considered a logical stroke treatment strategy. Theoretically, oxygen should be an excellent drug for treating stroke since it has distinct advantages over pharmaceutical agents: it easily diffuses across the blood–brain barrier, has multiple beneficial biochemical, molecular, and hemodynamic effects, it is well tolerated, and can be delivered in high doses without dose-limiting side-effects (except in patients with chronic obstructive pulmonary disease) (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006). Experimental studies have shown that supplemental oxygen favorably alters the levels of glutamate, lactate, bcl2, manganese superoxide dismutase, cyclooxygenase-2, and inhibits cell-death mechanisms such as apoptosis (Yin W, Badr AE, Mychaskiw G, Zhang JH , 2002), (Yin D, Zhou C,Kusaka I, Calvert JW, Parent AD,Nanda A, Zhang JH , 2003), (Wada K,Miyazawa T,Nomura N,Tsuzuki N,Nawashiro H, Shima K , 2001), (Menzel M, Doppenberg EM, Zauner A, Soukup J, Reinert MM,Bullock R , 1999), (Rockswold SB, Rockswold GL, Vargo JM, Erickson CA, Sutton RL, Bergman TA, Biros MH , 2001), (Zhang JH, Singhal AB, Toole JF , 2003), (Badr AE,Yin W,Mychaskiw G, Zhang JH , 2001). Because the rationale for oxygen in stroke is so compelling, numerous groups have focused on it as a potential therapy. Hyperbaric oxygen therapy (HBO) has been widely studied because it significantly raises brain tissue partial pressure of oxygen (brain *pti*O2), a factor believed critical for effective neuroprotection (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006). Clinical improvement during exposure to HBO was observed nearly 40 years ago (Ingvar HD, Lassen NA , 1965).

CAUSES OF ISCHEMIC STROKE

Ischemic stroke occurs due to a multitude of underlying pathologic processes. The brain is such an exquisite reporting system that infarcts below the size that cause clinical signs in other organ systems can cause major disability if they affect brain. About 85% of all strokes are due to ischemia, and in the majority of ischemic stroke the mechanism responsible is understood (Fig. 11). An illustration of the causes of the majority of ischemic strokes is shown in Fig. 10, including atherosclerotic, cerebrovascular, cardiogenic, and lacunar (penetrating vessel) mechanisms. However, in about 30% of cases, the underlying causes are not known and these are termed cryptogenic strokes (W.J.Koroshetz, R.G.González, 2006). The pathways that lead to ischemic stroke are reviewed bellow.

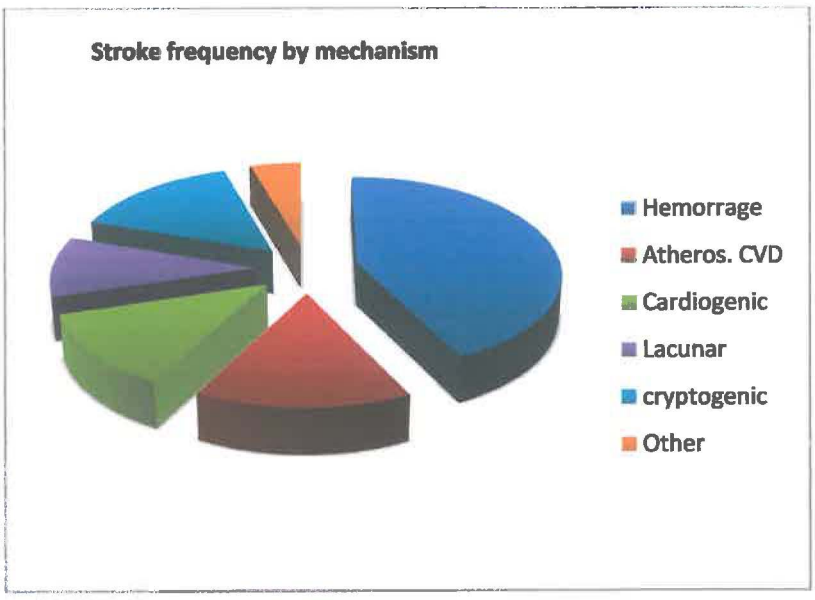


FIGURE 10 Stroke Frequency by Mechanism (W.J.Koroshetz, R.G.González, 2006)

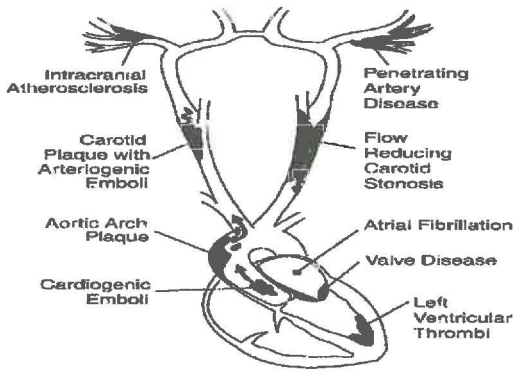


FIGURE 11 the most frequent sites of arterial and cardiac abnormalities causing ischemic stroke. (ALBERS GW, AMARENCO P, EASTON JD, SACCO RL, TEAL P, 2004)

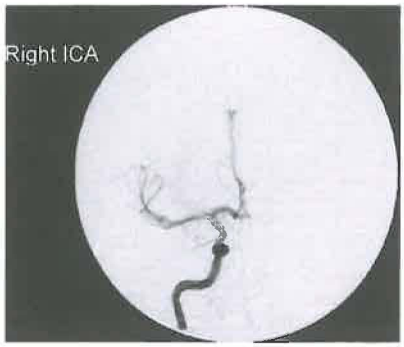


FIGURE12 Right Internal Carotid Artery

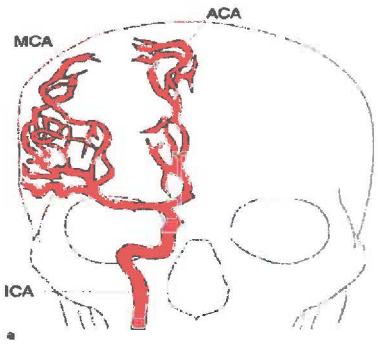


FIGURE 13 Internal Carotid Artery Feeds the Middle Cerebra Artery and Anterior Cerebral Artery

(W.J.KOROSHETZ, R.G.GONZÁLEZ, 2006)

RISK FACTORS

In numerous respects stroke is a preventable disorder. Prevention is the target of a variety of programs to reduce risk factors for stroke. The greatest stroke risk occurs in those with previous transient ischemic attack or previous stroke. For these patients risk factor reduction is essential and risk

may be associated with specific cardiovascular, cerebrovascular or hematologic disorders. Secondary vascular risk has been shown to decrease with treatment of hypertension and hyperlipidemia and the institution of antiplatelet drug treatment. Globally, hypertension is the most significant risk factor for stroke, both ischemic and hemorrhagic. Elevation in blood pressure plays a large role in the development of vascular disease, including coronary heart disease, ventricular failure, atherosclerosis of the aorta and cerebrovascular arteries, as well as small vessel occlusion. Diabetes mellitus ranks highly as a stroke risk factor. Unless it is quelled, the current epidemic of obesity is expected to fuel greater stroke risk in the near future. Hyperlipidemia, tobacco abuse, cocaine and narcotic abuse, and lack of physical exercise also contribute to population stroke risk. There is an increased incidence of stroke during seemingly nonspecific febrile illnesses (W.J.Koroshetz, R.G.González, 2006).

PRIMARY LESIONS OF THE CEREBROVASCULAR SYSTEM

CAROTID STENOSIS

Many stroke patients have atherosclerosis, indicating a link between cardiac and cerebrovascular disease. But it is difficult for clinicians to predict the likelihood of stroke using signs and symptoms of heart disease. For instance, carotid bruits are more reliably predictive of ischemic heart disease than of stroke (W.J.Koroshetz, R.G.González, 2006).

PLAQUE

A carotid plaque's variable composition may affect the associated stroke risk. Plaque is often echo dense and calcified, and can be formed by the homogenous deposition of cholesterol. Plaque is dangerous not only because of its stenotic effects – plaque may rupture or dissect at the atherosclerotic wall, showering debris into the bloodstream, leading to multiple embolic cerebral infarcts downstream of the plaque. The ruptured, ulcerated plaque can also be a source of thrombus formation in that the anticoagulant properties of the endothelial surface are locally disrupted. Using transcranial Doppler, a number of groups have shown increased frequency of microembolic signals in the ipsilateral MCA in the days after symptom onset in patients with carotid stenosis. Inflammation in the plaque wall has been postulated to influence thrombus formation in myocardial infarction (MI) as well as stroke. Recent studies have focused on the possibility that infection in the plaque contributes to thrombus formation and subsequent stroke or MI. *Chlamydia* particles have been recently discovered in carotid and coronary plaques (W.J.Koroshetz, R.G.González, 2006).

ATHEROSCLEROSIS LEADING TO STROKE

An atherosclerotic lesion at the origin of the ICA can lead to stroke. The first pathway is a result of progressive narrowing of the ICA until the sluggish blood flow promotes the formation of a thrombus at the residual lumen, which results in complete occlusion. The acute occlusion may be symptomless if excellent collateral circulation exists along the circle of Willis and between leptomeningeal vessels; alternatively it may cause a

large hemispheric stroke if collaterals are poor. The second pathway, termed "artery to artery" embolism, is a common pathway for MCA distribution stroke in patients with severe extracranial internal carotid stenosis. Commonly, this occurs at the time of ICA occlusion (W.J.Koroshetz, R.G.González, 2006).

COLLATERAL PATHWAYS IN THE EVENT OF CAROTID STENOSIS OR OCCLUSION

In the pathway shown above (Fig. 12), leptomeningeal collateral blood sources traveling over the surface of the brain bring blood from the distal ACA branches into the distal MCA branches. This type of leptomeningeal collateral flow can also come from the posterior cerebral artery (PCA) branches to fill the distal MCA. Flow from the vertebrobasilar system can fill the distal ICA and its branches through the posterior communicating artery (PCoA). The potential for collateral flow in the case of carotid occlusion depends on the vascular anatomy of these alternative pathways. When collateral flow is not sufficient, ischemia occurs in the border zone (sometimes called "watershed") regions between the ACA/MCA and MCA/PCA (W.J.Koroshetz, R.G.González, 2006).

TRANSIENT NEUROLOGICAL DEFICITS

Reoccurring transient neurological deficits also occur commonly in patients with MCA or intracranial carotid stenosis. These deficits generally last for less than 3min and include transient monocular blindness as well as transient

hemispheric neurologic deficits. Their pathologic basis is unknown, though in some cases of transient monocular blindness there is evidence of low flow (the "box car" appearance of red cell clumps separated by clear space) in the retinal arterioles. The retina may also contain highly refractile cholesterol emboli called Hollenhorst plaques. In many instances of severe carotid stenosis or occlusion, the intracranial collateral flow is sufficient to perfuse the brain and prevent ischemia (W.J.Koroshetz, R.G.González, 2006).

INTRACRANIAL ATHEROSCLEROSIS

Atherosclerosis can also occur intracranially to cause focal or multifocal stenosis in the siphon portion of the ICA, the MCA stem, the branch points of the major MCA branches, the ACA, A1 and A2 branches, the P1 and P2 segment of the PCA, the distal vertebral artery, the vertebral artery origin, the vertebrobasilar junction, and the basilar artery. Microatherosclerotic plaques can occur as described above in the proximal portion of the penetrator arteries arising from the major vessels at the base of the brain. They are not seen in the leptomeningeal vessels over the cortex. Atherosclerosis in the intracranial portion of the carotid and in the MCA causes multiple strokes in the same vascular territory. It may also cause "slow stroke" syndrome, in which there is progressive worsening of focal cortical ischemic symptoms over days or weeks. In addition, the penetrator arteries flowing to the deep white matter and striatum originate from the MCA stem (M1) and may be occluded in patients with severe MCA stenosis. Atherosclerosis in the intracranial portion of the ICA and the MCA is more common in African Americans and Asian Americans for unknown reasons. Additional common sites for atherosclerotic occlusion include the origin of the vertebral artery, the distal vertebral and vertebrobasilar junction, the mid-

basilar artery, and the proximal PCA. Unlike ICA disease, severe atherosclerotic stenosis in the distal intracranial vertebral and basilar arteries can cause stroke via thrombotic occlusion of local branches as well as artery-to-artery embolus to the top of the basilar artery or the PCA(s). Low flow in the basilar artery can lead to thrombus formation with occlusion of one brainstem penetrator vessel after another. Basilar thrombosis is not rare and is fatal because brainstem function is completely dependent on this vascular supply. Low flow to the basilar artery can also be caused by vertebral disease. Sometimes one vertebral artery is small and terminates as the posterior inferior cerebellar artery, never making the connection to the basilar artery. Other times, one vertebral artery is occluded. In these two circumstances, flow-limiting disease in the dominant or remaining vertebral artery may then produce basilar ischemia. Thrombus at the site of vertebral artery stenosis can also dislodge and cause embolic stroke in the distal basilar artery or PCA territory. In patients with left subclavian artery occlusion, the left vertebral artery commonly originates distal to the occlusion. This can result in the subclavian steal syndrome, in which blood flows in a retrograde direction down the vertebral artery to supply the arm. This anatomic condition is most frequently asymptomatic, but can result in low flow in the basilar artery during arm exercise. In some patients with longstanding hypertension there is a dramatic dilatation of the intracranial vessels called "dolichoectasia." Basilar artery dolichoectasia can cause compression of the brainstem or cranial nerves. Thrombus can also form in these much dilated vessels leading to basilar-branch thrombotic occlusion or distal embolic stroke (W.J.Koroshetz, R.G.González, 2006).

AORTIC ATHEROSCLEROSIS

Atherosclerotic disease of the aorta is also likely to increase stroke risk. Transesophageal echocardiographic images can show plaque or thrombus on the aortic wall with dramatic flapping of a thrombus within the aortic lumen. Aortic atherosclerosis is a major cause of stroke during coronary artery bypass grafting; when the aortic cross clamp is released, atherosclerotic debris fills the aorta. Atherosclerotic emboli also occur as complications after coronary and aortic angiography due to vessel wall trauma from the catheter. So-called cholesterol emboli disease can cause multiple strokes as well as joint pain; livedo reticularis skin rash, reduced renal function, and seizures. These cholesterol embolic strokes may not be amenable to thrombolysis. Type I aortic dissection is one of the most difficult vascular lesions to manage in the presence of major stroke. The patient may present with chest pain and asymmetric pulses. Stroke may occur in the distribution of any major cerebral arteries because the dissection can involve both carotid and vertebral origins. Since rupture into the chest or extension of dissection into the pericardium or coronary origins is fatal, thrombolysis or anticoagulation cannot be used (W.J.Koroshetz, R.G.González, 2006).

RISK FACTORS FOR ATHEROSCLEROSIS

Hypercholesterolemia, family history of atherosclerotic disease, diabetes, homocysteinemia, elevated apolipoprotein a, hypertension, and smoking are all risk factors for generalized atherosclerosis. Inflammatory markers in the

plaque and the systemic circulation are currently under study for their role in triggering symptoms in patients with atherosclerosis.

EXTRA-CEREBRAL ARTERY DISSECTION

Extra-cerebral artery dissection is commonly responsible for stroke in young persons, including children. In adults, dissections tear the intima, and blood enters the wall of the vessel between the intima and the media. This blood causes the vessel wall to balloon outward, and compresses the lumen. If stroke results from this condition, it is most often caused by embolus; a thrombus forms at the tear site and is swept up the vessel into the brain. Dissection may also cause complete occlusion of the vessel and impair cerebral perfusion. The outwardly distended vessel wall may also compress nearby structures. In carotid dissection at the base of the skull, compression palsies of cranial nerves IX, X, XI, and XII are sometimes seen. Carotid dissection can also interrupt the sympathetic nerve fibers that surround the carotid, causing a Horner's syndrome ptosis and miosis. The dissection site can be high up in the neck, often extending to the point where the ICA becomes ensheathed in the dura at the entry site into the petrous bone. Dissection also occurs in association with redundant looping of the carotid artery. Vertebral artery dissection commonly occurs where the vessel passes over the C2 lateral process to enter the dura.

Symptoms:

Patients with carotid or vertebral dissection commonly present with pain. In extracranial carotid dissection the pain is localized to the region above the brow in front of the ear, or over the affected carotid. In vertebral dissection the pain is usually in the C2 distribution, ipsilateral posterior neck, and

occipital regions. Extracranial cerebral artery dissection occurs with massive trauma as well as minor neck injuries. It also occurs with seemingly trivial incidents, such as a strong cough or sneeze, chiropractic manipulation, hyperextension of the neck during hair washing, etc. In some cases, it appears to occur without known precipitants.Disorders of collagen such as fibromuscular dysplasia, Marfan's syndrome, and type IV Ehlers–Danlos syndrome are also associated with dissection. Arterial dissection can result in the formation of a pseudo-aneurysm. Rupture of dissected vertebral arteries into the subarachnoid space is more common in children. Rupture of dissected carotid artery pseudo- aneurysms into the neck or nasal sinuses is generally rare. Dissection can occur intracranially and, on rare occasions, can spread intracranially from a primary extracranial origin.

PRIMARY CARDIAC ABNORMALITIES

ATRIAL FIBRILLATION

Atrial fibrillation (AF) is a major risk factor for debilitating stroke due to embolism. The Framingham Stroke Study estimated that 14% of strokes occurred because of AF. The prevalence of AF is high and increases with age, peaking at 8.8% among people over the age of 80 years. The risk of stroke in patients with AF also increases with age: as many as 5% of patients over 65 with AF suffer embolic stroke. These emboli often originate as a mural thrombus, usually harbored by the fibrillating atrium, and more specifically the atrial appendage, because of its potential for regions of stagnant blood flow. Anticoagulation with warfarin has been shown to

decrease stroke risk in elderly patients with AF or younger patients with concomitant heart disease, reducing the risk of thrombus formation. In the evaluation of the patient with AF who experiences a stroke, it is important to determine whether the prothrombin time is elevated. The risk of warfarin-associated major hemorrhage, mostly intracranial, is approximately 0.5% per year. A hemorrhagic stroke, however, can still occur with a well-controlled prothrombin time.

MYOCARDIAL INFARCTION

Myocardial infarction (MI) commonly causes intraventricular thrombus to form on the damaged surface of the endocardium. Acute anterior wall infarction with aneurysm formation is especially associated with thrombus formation and stroke. Poor left ventricular function and ventricular aneurysm is also associated with increased risk of embolic stroke.

VALVULAR HEART DISEASE

Atrial fibrillation with mitral valve disease has long been considered a stroke risk factor. Mechanical prosthetic valves are prime sites for thrombus formation; therefore, patients with these valves require anticoagulation. Bacterial endocarditis can cause stroke as well as intracerebral mycotic aneurysms. Inflammatory defects in the vessel wall, when associated with systemic thrombolysis and anticoagulation, rupture with subsequent lobar

hemorrhage, and precipitate stroke. Nonbacterial, or "marantic," endocarditis is also associated with multiple embolic strokes. This condition is most common in patients with mucinous carcinoma and may be associated with a low-grade disseminated intravascular coagulation. A nonbacterial endocarditis, called Libman–Sacks endocarditis, occurs in patients with systemic lupus erythematosus (SLE). The role of mitral valve prolapse in stroke remains controversial. Strands of filamentous material attached to the mitral valve seen by echocardiography have recently been reported as a risk factor for embolic stroke.

PATENT FORAMEN OVALE

Patent foramen ovale (PFO) occurs in approximately 27% of the population. Though the left-sided pressures are usually higher than those on the right, the flow of venous blood toward the foramen ovale can direct some blood to the left side of the heart. Increases in right-sided pressures, which can occur with pulmonary embolism or the Valsalva maneuver, increase blood flow from right to left atrium.PFO has been detected with increased incidence (up to 40%) in young persons with stroke. It is thought that venous clots in the leg or pelvic veins loosen and travel to the right atrium, and then cross to the left side of the heart causing embolic stroke. This conclusion is supported when stroke occurs in the context of deep vein thrombosis (DVT) or pulmonary embolus (PE) in a patient with PFO.

CARDIAC MASSES

Atrial myxoma is a rare atrial tumor that causes multiple emboli of either thrombus or myxomatous tissue. When the myxomatous emboli occur from the left atrium, they may cause the formation of multiple distal cerebral aneurysms with risk of hemorrhage. Fibroelastoma is a frond-like growth in the heart that is also associated with a high stroke risk.

EMBOLIC STROKE

THE LOCAL VASCULAR LESION

The occlusion of an intracerebral vessel causes local changes in the affected vessel and its tributaries. There is also a vascular change in the microcirculation supplied by these vessels. As an embolus travels toward the brain, it is forced into progressively narrower vessels before it lodges in a vessel too small for it to pass. The initial shape of emboli and their course are not well known. Because the major vessels of the Circle of Willis have lumen diameters of only 1–2 mm, dangerous clots need not be very large. Some clots that have a string shape and curl, like those from a deep vein, become temporarily stuck at turns in the vessel, eventually becoming compacted into a plug when they finally lodge. The vessel is often distended. Symptoms localized to basilar branches sometimes occur in the moments before a top of the basilar ischemic syndrome occurs. Called the "basilar

scrape," this is thought to result from temporary ischemia caused by the embolus as it travels up the vertebral and basilar vessels to the bifurcation at the top of the basilar artery. Emboli lodge at branch points, such as the T-like bifurcation of the basilar into two posterior cerebral arteries, and the T-like bifurcation of the carotid into the ACA and MCA. The fork of the MCA stem into the two or three divisions of the MCA is another common lodging site for emboli. Small branches coming off the large vessel at these sites will be occluded. There are a number of thin penetrator vessels that supply the midbrain and the overlying thalamus that are occluded in the top of the basilar embolus. The lumen of the anterior choroidal artery is in the distal carotid. Coming off the middle cerebral stem are penetrators to the striatum and internal capsule. Ischemia in these vascular territories that have little collateral flow channels can quickly lead to infarction as compared to ischemia in the cerebral cortex, which can receive blood flow via leptomeningeal collaterals.

MICROVASCULAR CHANGES IN ISCHEMIC BRAIN

In contrast to the situation in occluded small vessels, the vascular tree distal to an occlusion in a main cerebral vessel will not be occluded by the clot. In order to keep blood flow at normal levels, the distal vascular tree undergoes maximal vasodilatation. This vasodilatation is in part regulated by the action of nitric oxide on the vascular wall. Ischemic vasodilatation will attract collateral flow to the cortex from other vascular channels through leptomeningeal vessels. In the fully dilated bed, the cerebral blood flow will be driven by the blood pressure. As blood flow falls in the microvessels there is potential for microvascular thrombus formation. The endothelial surface of the microvascular circulation normally has an anticoagulant

coating. Under ischemic conditions, it becomes activated to express white blood cell adhesion molecules. White blood cells attach to the vessel wall and may mediate microvascular injury and microthrombosis. In such a case, despite the recanalization of the main feeder vessel, there is "no reflow"of blood to the tissue. This loss of accessibility of the microvasculature to the blood pool and decreased cerebral blood volume are closely linked to infarction. In animal studies, stroke size is decreased if white blood cell counts are reduced or drugs are given to block white cell adhesion. Free radical production by the white blood cells is considered an important mediator of vessel-wall injury in stroke. Damage to the vessel wall is manifested as hemorrhage into the infarct. Hemorrhagic conversion of embolic stroke is very common when examined by magnetic resonance imaging (MRI) sequences sensitive to magnetic susceptibility of the iron. In hemorrhagic conversion there are multiple small hemorrhages in the infarct that may not be apparent on CT scan or may be seen as a hazy or stippled increase in signal intensity. Large hemorrhages can also occur in the infracted tissue. The latter are more common in large strokes that include the deep white matter and basal ganglia. As opposed to hemorrhagic conversion, which is usually not accompanied by clinical change, the large hematoma in the infracted zone is often associated with worsened neurologic deficit. These hematomas frequently exert considerable mass effect on adjacent brain tissue and can increase intracranial pressure (ICP) and distort midbrain and diencephalic structures. Since these hemorrhages more commonly occur in the larger strokes, they often compound the mass effect due to ischemic edema. Hematoma formation is the major risk of thrombolytic therapy. The use of drugs that impair hemostasis (anticoagulants) may increase the probability of bleeding into a vascular territory with an injured vascular wall. Hemorrhage occurs when the blood flow and blood pressure are restored in a previously ischemic zone. The injured vascular wall is incompetent to with stand the hydrostatic pressure and the return of oxygen and white blood cells may also intensify the reperfusion injury at the vascular wall. The vascular

wall also regulates the flow of large molecules from the vascular space to the intercellular space (the so-called blood–brain barrier). In ischemia, there is net movement of water into the brain tissue. This is the basis of the increased T2 signal on MRI and the low density on CT in the first few days after stroke. At variable times after stroke, contrast imaging studies show that large molecules also cross into the brain tissue. The net water movement into brain, ischemic edema, can lead to secondary brain injury as a result of increased ICP and the distortion of surrounding tissues by the edematous mass effect. Mass effect, causing clinical worsening and classical herniation syndromes, is not uncommon in patients with large MCA strokes.

MCA EMBOLUS

An embolus to the MCA is common and can cause a catastrophic stroke. It is also amenable to rapid therapy. For these reasons, special emphasis is placed here on this stroke subtype. As discussed above, carotid stenosis and occlusion cause stroke by arteryto- artery embolus into the MCA territory or by causing a low-flow state. This gives rise to the clinical syndrome of MCA stroke. Distinguishing features of carotid stenosis include the common occurrence of multiple stereotypic spells of transient ipsilateral hemispheric or monocular dysfunction. In addition, in carotid stenosis multiple emboli may occur over a short period of time. In some cases of embolus to the MCA from a severely stenotic carotid, the embolus may be less well tolerated and the stroke more severe due to the lower perfusion pressure above the carotid lesion. Embolus from the carotid to the MCA can also occur from the stump of a completely occluded carotid. If the occlusion is hyperacute, then it is often possible to dissolve the fresh clot in the extracerebral carotid with urokinase and advance the catheter to treat the intracerebral clot. This can be

followed by angioplasty of the carotid stenosis. However, if the carotid occlusion is more chronic, the organized clot extends up from the occlusion in the neck intracranially and may prevent passage of the catheter. This will preclude intra-arterial thrombolysis of the MCA clot.

BORDERZONE VERSUS EMBOLIC INFARCTIONS

Carotid stenosis can also cause low-flow stroke when the collateral flow from the anterior communicating artery (ACoA), PCoA, and retrograde through the ophthalmic artery is insufficient to perfuse the ipsilateral hemisphere. Low flow causes symptoms and infarction in the distal cortical watershed territory between the distal branches of the ACA, MCA, and PCA. The actual boundaries between these territories may shift due to increased flow through the ACA or PCA to supply the MCA. The classic presentation is called the "man in the barrel syndrome." The watershed ischemia causes dysfunction in the regions for motor control of the proximal arm and leg. There may be an aphasia known as "transcortical aphasia" due to disconnection of the laterally placed language areas and medial cortex. In transcortical aphasia, repetition is relatively preserved. In transcortical motor aphasia there is hesitant speech but preserved comprehension. In transcortical sensory aphasia, comprehension is more severely impaired than speech. Cortical watershed stroke is seen on imaging as a thin strip of infarction that runs from the posterior confluence of the MCA, ACA, and PCA branches in the posterior parietal cortex extending forward on the upper lateral surface of the cerebrum. On axial scans there is a small region of stroke on each of the upper cuts; only by mentally stacking the images does the examiner appreciate that the lesions are contiguous and form an anterior to posterior strip of stroke. The strip overlies the motor areas for control of

the proximal leg and arm. A cortical watershed infarction is not entirely specific for low flow, because it can also be caused by showers of microemboli that lodge in the region of neutral hydrostatic pressure. In addition to the cortical watershed, there is also an internal watershed formed by the junction of the penetrator arteries from the MCA and the leptomeningeal cortical vessels that enter the cortex and extend into the white matter. This watershed again forms a strip that lies in the white matter just above and lateral to the lateral ventricle. Instead of a strip of contiguous stroke the internal water shed region usually undergoes multiple discrete circular or oval shaped strokes that line up in an anterior to posterior strip. Internal watershed infarction may be more specific for low-flow stroke.

LACUNAR STROKES

Penetrator vessels come off the basilar artery, the middle cerebral stem, and the PCA at right angles to the parent vessel. Small-vessel occlusive disease is almost entirely related to hypertension and is characterized pathologically by lipohyalinosis and fibrinoid necrosis of small 80- to 800-*m*m penetrator vessels. Occlusion of these penetrators causes small infarcts, termed lacunars, in their respective vascular territories, most commonly in the caudate, putamen, external capsule, internal capsule, corona radiata, pontine tegmentum, and thalamus. Hypertensive hemorrhage occurs in these same regions and is due to the same hypertensive changes in the penetrator vessels. The deficits caused by these small strokes are a function of their location. Because the penetrator vessels supply deep white matter tracts as they converge in the internal capsule or brainstem, the consequence of lacunar stroke is often related to disconnection of neural circuits. Lacunar strokes are especially common in patients who have diabetes in addition to

hypertension. Lacunar strokes can cause immediate motor and sensory deficits, though many patients recover considerable function in the weeks or months following lacunar stroke onset. In the National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study (NINDS rt-PA Study), 50% of patients returned to a normal functional level within 3 months without rt-PA treatment. In the group receiving rt-PA, the probability of good recovery increased to 70%. A number of clinical syndromes commonly occur due to lacunar strokes (see Table 1). However, the clinical symptoms may not be specific for the chronic occlusive disease of the small penetrator vessels described above.

Of special importance is the infarct in a penetrator territory caused by disease of the parent vessel. In some cases, the penetrator stroke is only one, sometimes the first, of many regions to undergo infarction due to major vessel occlusion. In basilar artery occlusive disease, ischemia in the distribution of a single penetrator may occur as the "opening shot." On succeeding days, the origin of multiple penetrators becomes occluded due to the propagation of mural thrombus in the vessel. In addition, atherosclerosis in the parent vessel may narrow the lumen at the origin of the penetrators. Atherosclerosis may also occur in some of the larger penetrators. Large strokes, or giant lacunes, occur as a result of the occlusion of multiple penetrators with occlusive disease in the parent vessel. This is particularly common in the MCA territory where leptomeningeal collateral flow preserves the cortex, but absence of collateral flow to the penetrator territory results in infarction. In some cases, showers of small emboli cause penetrator strokes as well as cortical strokes. Small emboli may also reach these vessels. Chronic meningitis due to tuberculosis or syphilis commonly causes stroke in the penetrator territory due to inflammation around the parent vessel at the base of the brain with occlusion of the thin penetrators exiting through the inflammatory reaction.

Clinical lacunar syndrome and infarct location	
Pure motor hemiparesis involving face, arm, and leg	Contralateral posterior limb internal capsule or overlying corona radiata
Contralateral pontine tegmentum	
Pure unilateral sensory loss involving face, arm, and leg	Contralateral thalamus
Hemiparesis with homolateral ataxia	Contralateral thalamocapsular region
Upper third of the contralateral medial pons	
Dysarthria, clumsy hand	Contralateral lower third of the medial pons
Hemisensory loss and homolateral hemiparesis	Genu of the internal capsule
Sensory loss around corner of mouth and homolateral weakness of hand	Thalamocapsular region

Table 1clinical Lacunar Syndrome and Infarct Location (W.J.Koroshetz, R.G.González, 2006)

OTHER CAUSES OF STROKE

INFLAMMATORY CONDITIONS

Primary granulomatous angiitis of the central nervous system causes progressive ischemic brain injury. Blood vessels of various sizes are affected by inflammation and, on occasion, hemorrhage occurs in addition to stroke. Granulomatous angiitis can occur in the MCA ipsilateral to V1-distribution Herpes zoster or in the vertebral after C2-distribution Herpes zoster. The cerebrospinal fluid (CSF) often shows signs of inflammation. Diagnosis is commonly made after a biopsy of the leptomeningeal vessels demonstrates the granulomatous inflammation. When caught in its early stages, treatment with cyclophosphamide and/or steroids can reverse the process. Left untreated, the disease is usually fatal and causes severe diffuse or multifocal brain injury.

Systemic lupus erythematosus (*SLE*) has a variety of presentations in the nervous system. Stroke-like events can occur, along with seizures and

encephalopathy due to a small vessel vasculopathy. A circulating factor that increases the partial thrombin time (PTT), so-called lupus anticoagulant or anticardiolipin antibody, is associated with arterial thrombosis. A nonbacterial endocarditis may be a cause of embolic stroke.

Temporal arteritis is a giant cell arteritis seen in older adults with an elevated erythrocyte sedimentation rate, an elevated fibrinogen level, and a thickened wall of the extracranial carotid branches. Temporal arteritis can cause headache, tenderness over the temporal artery, jaw claudication, and transient visual loss. It is sometimes associated with polymyalgia rheumatica. It occasionally affects the vertebral artery.

Takayasu's arteritis is a giant cell arteritis of the large vessels off the arch of the aorta. It can cause occlusive disease in the carotid and the vertebrals, leading to stroke. Polyarteritis nodosa has rarely been reported to affect intracranial vessels. Sickle cell disease causes extracranial carotid stenosis or occlusion. The beta amyloid that is deposited in plaques of patients with Alzheimer's disease can also infiltrate the walls of the small blood vessels that supply the cortex. This *amyloid angiopathy* is a common cause of lobar hemorrhage in the elderly, most of whom do not have Alzheimer's disease. Some patients present with transient neurologic deficits prior to their hemorrhage. Small microinfarctions can occur in the cortex, in addition to multiple hemorrhages. Hemorrhage is found to occur in those patients who have a combination of amyloid deposition in the vessel wall and fibrinoid necrosis of the vessel wall. Amyloid angiopathy is considered a major risk factor for intracerebral hemorrhage in patients receiving thrombolytic drugs for MI or stroke. *Moya-moya* disease is an unusual condition causing progressive stenosis and occlusion of the internal carotid and the vessels of the Circle of Willis. Recurrent stroke as well as occasional hemorrhage characterizes the clinical syndrome. A proliferation of collateral vessels into the deep penetrator territory leads to an appearance of a"puff of smoke" on direct angiography.

VENOUS SINUS THROMBOSIS

Venous sinus thrombosis can cause focal neurologic deficits, often with seizures, headache, and other signs of raised intracranial pressure. Venous strokes are frequently hemorrhagic and located in the proximity of the occluded sinus– parasagittal in a sagittal sinus thrombosis, temporal lobe in a transverse sinus thrombosis, and thalamus in a straight sinus thrombosis. Venous sinus thrombosis is seen in patients with hypercoagulable state or as a consequence of infiltration of the major sinus by tumor or infection.

VASOSPASM IN THE SETTING OF SUBARACHNOID HEMORRHAGE

Subarachnoid hemorrhage (SAH) is most commonly caused by rupture of an intracranial aneurysm. It can result in vasospasm that may cause ischemia and infarction. Vasospasm due to SAH is thought to occur in the majority of cases of SAH, but is symptomatic in about a third of this population. Permanent neurological injury may occur in 10% or more. Vasospasm peaks around 1 week after SAH, but it can be seen as early as 3 days or as late as 3 weeks after the initial event. The underlying mechanisms are not understood, but vasospasm is clearly related to the amount of blood in the subarachnoid space.

MIGRAINE

Epidemiological studies have demonstrated that migraine is associated with ischemic stroke independent of other risk factors. The mechanism is unknown, but potential factors include vascular hyper-reactivity, and sensitivity to or increased amount of vasoactive substances.

PRIMARY HEMATOLOGIC ABNORMALITIES

Clotting systems disorders that cause systemic bleeding are associated with increased risk of intracerebral hemorrhage. Coumadin use is perhaps the most common cause of intracerebral hemorrhage, followed by thrombocytopenia. Thrombotic thrombocytopenic purpura (TTP) is most commonly manifested as ischemic stroke and should be treated by emergency plasmapheresis, which can reverse the microvascular thrombosis. Hypercoagulable states, such as protein C or S deficiency and Factor V Leiden mutation, increase the risk of venous sinus thrombosis. Arterial and venous occlusions occur in anticardiolipin syndrome along with fetal wasting and livedo reticularis. A hypercoagulable state with venous sinus thrombosis commonly occurs in the post-partum period or in severely dehydrated patients.

HYPERBARIC OXYGEN THERAPY

Hyperbaric Oxygen Therapy is defined by the Committee on Hyperbaric Medicine as " A mode of medical treatment in which the patient is entirely enclosed in a pressure chamber and breathes 100% Oxygen at a pressure greater than 1 atmosphere absolute (ATA) ". The unit of Pressure is ATA, 1 ATA is equivalent to 760 mm of Mercury or pressure at sea level.

The application of HBO depends on the physical properties of gases under pressure, specifically, oxygen at pressure greater than 1atm. Oxygen is essential in a variety of enzymatic, biochemical, and physiologic interactions that promote normal cellular respiration and tissue function. Mono-oxygenize, intradioxygenase, and interdioxygenase are specific enzymes that recruit oxygen as a cofactor to perform required biologic processes. Collagen deposition and synthesis depend on an oxygen dependent prolyl-hydroxylase hydroxylation of proline. Angiogenesis and epithlization are also oxygen dependent.

Over the past 40 years Hyperbaric Oxygen therapy (HBO) has been recommended and used in a wide variety of medical conditions, often without adequate scientific validation of efficacy or safety. Consequently a high degree of medical scepticism had developed regarding its use (Leach R M, Rees PJ, Wilmshurst P. , 1998). Over the last two decades, animal studies, clinical trials have produced reasonable scientific evidence or well validated clinical experience. This has now produced a set of indications for which HBO is beneficial (Hampson NB. Chairman & Editor., 1999), (Grim PS, Gottlieb LJ, et al. , 1990). This has led to a renaissance of HBO, and hyperbaric facilities now form an important part of many hospitals all over the world. China leads with 2600 Hyperbaric Centers, Russia: 2000, Japan: 400, approx 200 in the UK, 400 all over Europe and approx 800 in the US.

In Asia: Malaysia 5 centers, Middle East: 10, 1 in Srilanka and 1 emerging in Bangladesh (Tarun Sahni, S. Hukku, Madhur Jain, Arun Prasad, Rajendra Prasad, Kuldeep Singh, 2004).

In 1999 there were 500 hyperbaric facilities in USA and presently 800 with an annual increase in the number of Hyperbaric Centers and increase in patients at the rate of 15 and 620 respectively and this same rate of growth continues (Tibbles PM, Edelsberg J S. , 1996). With the recent approval of HBO as treatment for diabetic foot lesions, the above mentioned figures will likely double. With this continuing growth all over the world Hyperbaric Medicine has found a distinct role in the modern era of evidence based medicine.

THE HISTORY OF HYPERBARIC OXYGEN THERAPY

Attempts in the use of increased atmosphere pressure, for medical therapy has been around for hundreds of years. Vague accounts of this treatments dates back to the fifth century BC. The very first sealed chamber known as a DOMICILIUM was belt by Henshaw, a British clergyman as early as 1662. He made use of a system of organ bellows and found a way to adjust pressure within a sealed chamber. The principle that was used was that acute conditions would respond to elevated atmospheric pressures and chronic conditions to reduced atmospheric pressure (Henshow, 1664). The Domicilum compressed air (21% oxygen) for number conditions including inflammation, scurvy, arthritis, and rickets. No physical improvements were observed likely due to its low compression (Neumeister, 2005).

Thereafter, air-compression devices evolved in appearance and function. In the late 1700s Priestly discovered oxygen, consequently a pneumatic laboratory enriched with oxygen to treat chronic conditions such as leprosy was developed (Junod, 1834). In the early 1930s, the JUNOD reported improvement in patients with cardiorespiratory disorders here a compression chamber made of copper was used at 2 atm of pressure. These lead to a rapid establishment of several "pneumatic institutes" in Europe. These institutes used chambers that could reach pressures of 2 or more atm and accommodate a capacity of up to 10 people per session. Pneumatic spas came to North America in 1860, with the first compression chamber built in Oshawa, Ontario, Canada (Neumeister, 2005).

By 1878, much knowledge had been gathered about the effects and uses of hyperbaric oxygen therapy. It was also discovered that the use of compressed air could facilitate other methods. In 1879 a French surgeon Fontaine published his findings on the effects of hyperbaric treatment he reported improved patients outcomes due to increased oxygenation and decreased postoperative vomiting and cyanosis. Noted where also easier reduction of herniations. Furthermore he told of his mobile hyperbaric chamber's favorable effects on the outcome of surgery. Fontaine created a mobile compressed operating suit that took advantage of a basic law of physics (Henry's law), which states that the solubility of a gas in a liquid is proportional to the pressure of the gas over the solution, provided that no chemical reaction occurs. By raising the atmospheric pressure within the chamber, Fontaine was able to increase the amount of oxygen carried by the patient's bloodstream during the administration of nitrous oxide anesthesia. This prevented blood oxygen levels from falling too low as typically happened with surgically acceptable depths of anesthesia (Fontaine, 1879). The introduction of therapeutic compression chambers that made used of electric power for its operation dates back to 1891 in the US by Corning.

Corning. This chamber was used for the treatment of nervous and mental afflictions (Corning, 1891).

In 1918 during the Spanish flu epidemic which resulted in more than 500,000 deaths, many of which were in a cyanotic state. Orville Cunningham came across a discovery. He noted that patients with certain cardiovascular disorders who dwelled at high altitudes fared less well than comparable patients living closer to sea level. During this time Dr Cunningham, successfully treated a rather sick resident physician suffering from influenza and was near death from lack of oxygen secondary to restricted lung function. This subsequently led Dr Cunningham to develop a cylindrical hyperbaric chamber approximately 3 meters in diameter by 27 meters in length, in which he successfully treated numerous conditions with remarkable outcomes (Jacobson JH and others. , 1965). This in turn led to the reinforcement of the credibility of the compression chamber during treatment of patients ill due to influenza (Cunningham, 1927).

Cunningham's fortunes took another upturn following the recovery of a patient afflicted with kidney disease-uremic state. Ascribing his dramatically improved health to hyperbaric therapy, the grateful patient built for Cunningham a chamber fit for a king. This chamber -- built in Kansas City in 1921 -- was a hollow steel ball of approximately 20 meters in diameter and equipped with a smoking lounge, dining facilities, rich carpeting, and private quarters (Arago., 1845). Conditions such as hypertension, diabetes, syphilis, and cancer were treated here until 1930, when it met an undignified end. Its continued survival depended on demonstrable successes. Cunningham postulated that anaerobic bacteria (bacteria preferring low oxygen environments) were responsible for cancers, high blood pressure, and many other conditions. Based on this, he predicted that all would resolve at elevated atmospheric pressures that increase blood oxygen levels. Unfortunately, the local medical society did not find the results compelling

and closed the hyperbaric hospital for a lack of scientific evidence or merit (Cunningham, 1927).

The promotion of hyperbaric medicine came again into effect when elevated interest in underwater activities arose amongst the military. Studies in the 1930s suggested that supplementary oxygen could play an important role in treating decompression sickness. However, because oxygen could be explosive, three decades passed before equipment was developed that could safely handle its administration. Oxygen breathed under pressure forcibly washes nitrogen from tissues. Treatment protocols using hyperbaric oxygen therefore require substantially less time to complete than do those using only compressed air. Thus, hyperbaric oxygen remains the frontline instrument in the treatment of decompression sickness to date.

Hyperbaric oxygen first entered land-based medicine in the Dutch surgical realm with the concept of drenching tissue, which required pressurization of the entire operating theater. Dr. I.Boerema, a cardiovascular surgeon also thought of as, the father of modern-day hyperbaric medicine, fostered therepapeutic hyperbaric medicine by publishing his findings on the use of hyperbaric oxygen as an aid in cardiopulmonary surgery in 1956. In particular for congenital cyanotic disorders such as tetralogy of Fallot and transposition of the great vessels as well as for pulmonic stenosis. His hypothesis was based on the idea that by saturating the body tissues with oxygen, he would be able to extend the tissue survival time when clamping the major arteries (Boerema I and others. , 1956). The advent of more effective cardiopulmonary bypass techniques means that hyperbaric oxygen is no longer used for cardiac surgery. However, his discovery (with his colleague, Dr. Brummelkamp) that HBO inhibited the growth of anaerobic bacteria, and thus was an effective treatment for gas gangrene is still saving lives even today. In 1961 he subsequently published his findings (Brummelkamp, 1961). At the same time, Boeroma released an article, "Life

without blood," in which he elaborated the successful treatment of fatally anemic pigs with volume expansion and pressurized hyperoxgenation, hens the flurry of interest in therapeutic hyperbaric medicine (Boerema, 1960).

The discovery that Smith and Sharp unlashed in 1962 reported the enormous benefits of HBO in carbon monoxide poisoning (Smith G, Sharp GR, 1962). Fueled by early medical successes employing hyperbaric oxygen, the clinical community began deploying hyperbaric chambers at additional sites, such as at Duke University, New York Mount Sinai Hospital, Presbyterian Hospital and Edgeworth Hospital in Chicago, Good Samaritan in Los Angeles, St. Barnaby Hospital in New Jersey, Harvard Children's Hospital, and St. Luke's Hospital in Milwaukee, as well as in numerous international sites. Further benefits of hyperbaric medicine where recorded for the following conditions; split-thickness skin graft acceptance, flap survival and salvage, wound re-epithelization, and acute thermal burns. These studies subsequently lent credibility to the therapeutic use of hyperbaric oxygen therapy. Meanwhile, the academic community commenced high-profile international meetings, and reputable scientific medical bodies, such as the International Congress on Hyperbaric Oxygen and the Undersea Medical Society. Through these efforts, the fundamental principles governing the physiological effects of hyperbaric oxygen were derived, and practical issues pertinent to engineering and hyperbaric medicine came to the fore (National Academy of Sciences, National Research Council. , 1966).

During the 1970s, the practice of hyperbaric oxygen therapy experienced hard times because:

- more effective therapies such as cardiac surgery became available,
- efforts to use it for various medical conditions proved unsuccessful,
- Physicians who were high-profile HBOT advocates damaged its reputation and once again tarnishing the credibility of hyperbaric medicine.

However, respectable practices have been defined and established through further research, the development of textbooks and scholarly journals, and the activities of professional associations such as the Undersea and Hyperbaric Medical Society which as a result of the indiscriminate and inappropriate use formulated guidelines for the use of hyperbaric therapy.

Scientists and researchers working in this field continue to take great advantage of the angiogenic properties that occurs during increased oxygen gradients as a result of hyperbaric oxygen therapy. They conducted studies on subject of wound-healing such as foot wounds from diabetes, radiation ulcers and other ischemic wounds and likewise successfully treated them with the use of hyperbaric oxygen therapy. Prospective blinded randomized trials and well-executed laboratory studies continue to further define the role of hyperbaric therapy in medical therapeutics.

The undersea medical society changed in 1986, and was renamed Undersea and Hyperbaric Medical Society, in recognition of advances in hyperbaric treatments an approved certification of added competency in undersea medicine was issued by the American Board of Medical Specialists. Furthermore in 1991 The National Board of Hyperbaric Medicine Technology gave its first certification to hyperbaric technicians (Undersea and Hyperbaric Medical Society, 1999).

PHYSIOLOGICAL BASIS

The main principal underlining the application of hyperbaric oxygen therapy is its dependence on the physical properties of gases under pressure, specifically that of oxygen at pressure greater than 1 atm (Bassett BE, Bennett PB Hunt TK Ed., 1986). In order to promote physiological cellular respiration and tissue functions in a living organism numerous oxygen dependent interactions are required. Included among others are bio-chemical, physiological and enzymatic interactions. Examples of specific enzymes that recruit oxygen as a co-factor for the performance of essential biologic processes are mono-oxygenize, intradioxygenase and interdixoygenase. Similarly, synthesis and deposition of collagen is realized by an oxygen-dependent prolylhydroxylase hydroxylation of proline, likewise angiogenesis and epithelization. When we normally breathe air (with 21% O2) at sea level pressure, most tissue needs of Oxygen are met from the Oxygen combined to Hb, which is 95 % saturated. 100 ml blood carries 19 ml O2 combined with Hb and 0.32 ml dissolved in plasma. At this same pressure if 100% O2 is inspired, O2 combined with Hb increases to a maximum of 20 ml and that dissolved in plasma to 2.09 ml. The higher pressure during hyperbaric oxygen treatment pushes more oxygen into solution. The amount of O2 dissolved in plasma increases to 4.4 ml/dl at a pressure of 2 ATA and to 6.8 ml/dl at 3 ATA. This additional O2 in solution is almost sufficient to meet tissue needs without contribution from O2 bound to hemoglobinand is responsible for most of the beneficial effects of this therapy.

A review of diving physics and physiology is helpful in understanding the clinical applicability of HBOT (more details bellow under mechanism of action). Hyperbaric oxygen pressure is expressed in multiples of atmospheric

pressure at sea level, where 1 atm is about 760 mm Hg or 1 kilogram per square centimeter (Grim P, Gottlieb LJ, Boddie A, et al., 1990) (Tibbles P, Edelsberg J., 1996). Under normal circumstances at sea level, hemoglobin saturation in the arterial system is 97% and venous hemoglobin saturation is 70%. In representation of a physiologic maximum under normal conditions oxygen is loaded in the bloodstream to hemoglobin in which each gram of hemoglobin combines with 1.34 cm^3 of oxygen to form oxyhemoglobin. Moreover, 97, 5% of oxygen is carried in the bloodstream which is combined to hemoglobin and the remaining 2.5% is dissolved in plasma. The oxygen content can be calculated with the following equations (Camporesi EM, Mascia MF, Thom SR , 1996):

$$\text{Oxygen content} = 1.34 \text{ mL of } \frac{O2}{g} \text{ of Hb}$$

$$X_g \text{ of } \frac{Hb}{100\ cm3} \text{ x percent saturation}$$

Above 200 mL of mercury of pressure, the oxygen dissolved in plasma significantly increases.

This is calculated with the Henry law:

$$\text{Dissolved oxygen (vol \%)} = 0.0031 \left(\text{mL}\frac{O2}{100\ cm3} / \text{mmHg}\right)$$

$$X\ PaO_2$$

Under normal conditions with good perfusion at rest, tissues require 5-6 mL per dL of oxygen this can be dissolved or hemoglobin-bonded oxygen. Increasing the pressure to 3 atm increases the blood oxygen (dissolved oxygen not carried by hemoglobin) to 6mL per dL (Sheridan R, Shank E. , 1999) (Leach RM, Rees PJ, Wilmshurst P. , 1998). Likewise the increase in pressure reduces the volume of gases in the blood by virtue of Boyle's law (in an enclosed space, the volume of gas is inversely proportionate to the pressure exerted upon it) (Jain K, 1999) (Kindwall, 1999). When considering

the above illustrated oxygen content equation, oxygen content of blood in total under hyperbaric pressure can be calculated, it is equal to the oxygen content calculation plus the dissolved oxygen content. The average metabolic consumption of oxygen by humans at sea level is 6,6cm^2/100 cm^2 of blood. With all this in mind the following conclusion can be drawn: conditions in a hyperbaric chamber at pressures of 3atm while breathing 100% oxygen, the delivered oxygen content in total is more than the above stated metabolic requirement, which than leads us to the next conclusion that oxygen can be supplied under these conditions even if there is an absence of hemoglobin.

As oxygen is released from hemoglobin, carbon dioxide the byproduct of cellular respiration usually bonds with hemoglobin to form carboxyhemoglobin (20%) and carried in the blood. Carbon dioxide is further transported in the blood stream in the form of bicarbonate (75%) it can be dissolved in plasma (5%). According to Haldane effect, the saturation of hemoglobin with carbondioxide is dependent on deoxygenation. When we consider the state of hemoglobin under hyperbaric pressure, we notice that it remains saturated and therefore the $PaCO_2$ may increase. In patients where physiological respiratory compensatory mechanisms are present, extra carbon dioxide is exhaled and on the contrary, in cases where these mechanisms are pathologic, patients may develop significant carbondioxide retention as observed in chronic obstructive pulmonary diseases. This condition can be enhanced by an increase in the work of breathing exacerbated by hyperbaric treatments. Another reason for possible respiratory failure in patients who already are compromised with a raise in airway pressures is the fact that an increase in hyperbaric pressure leads to an increase in the work needed for breathing which is dependent on volume and pressure. The table 5 lists the effect that HBOT has on the CNS.

METHOD OF ADMINISTRATION

In general the delivery of Hyperbaric Oxygen pressure may be administered in one of two following chambers; a Monoplaced chamber and Multiplaced chamber (Kindwall, 1999) (Jain, 1999). Monoplaced chambers shelters a single patient at a given time. The patient is usually placed in the supine position the chamber is then pressurized with 100% Oxygen. These chambers are used to treat stable patients with chronic medical conditions, they are the less-costly option when considering initial setup and operation, but presents little or no opportunity for patient intervention during therapy. Current chambers intergrades a clear acrylic shell or view port that maximizes patient observation. In addition direct communication between the patient and the hyperbaric medicine technician or physician is made possible by communication device, which are intergraded within the chamber. On the contrary multiplaced chambers are designed to accommodate and treat many patients at the same time and also in cases when treating critically ill patients who require a medical attendant within the chamber as the chamber allows for patient-therapist intervention. These chambers are pressurized with compressed air that is piped directly from its source, while the patient breathes 100% Oxygen through special facemasks, endotracheal tubes and or tight fitted Oxygen Hoods. The therapeutic dosage may be affected due to the type of chamber in use, multiple chambers for example, using face masks or hoods that do not fit perfectly may result in dilution of 100 percent oxygen with room air (Jain .J. 1999). The treatment control panel controls the therapy and monitors the patient during the treatment.

A standardized method of the administration of Hyperbaric Oxygen Therapy in terms of duration, frequency and cumulative number of sessions has not

yet been found to date. Despite this, most therapy is given at 2 or 3 ATA and the average duration of therapy is 60 to 90 minutes. Number of therapies may vary from 3-5 for acute conditions to 50-60 for radiation illnesses (Sahni T, Singh P, John MJ. , 2003).

MECHANISM OF ACTION

A number of laws are applied when explaining the action mechanism of hyperbaric medicine. As stated above, in order to fully understand the mechanism of action used in hyperbaric medicine and thereby also its clinical applicability, a brief review of diving physics and physiology is necessary. The physiological bases of hyperbaric medicine are explained above. In this section, the two basic laws of physics which directly governs the principles of hyperbaric medicine are reviewed. The table opposite presents a list of pressure equivalents.

Pressure Equivalents
1 atmosphere (atm)
0.1013 megapascals (MPa)*
1.013247 bar (10 m of sea water)
33 ft of sea water (FSW)
34 ft of fresh water (FFW)
14.7 pounds per square inch (psi)
760 mm Hg

Table 2pressure Equivalents *Preferred Si (International System of Units) Measurement

BOYLE'S LAW: States that an inverse relationship exists between the pressure and volume of an ideal gas (PV=K).

The self-contained underwater breathing apparatus (SCUBA) diver is exposed to one atmosphere absolute (ATA) at sea level. Every 10 meters or 33ft of sea water (FSW) adds another atmosphere of pressure. As a diver ascends, the gas in her or his lungs expands due to the decreasing pressure. As an example, suppose a diver runs out of air at 20 meters of sea water (3 ATA). If the diver takes one last deep breath and rapidly ascends, the gas in the lungs will rapidly expand and potentially rupture the lungs. Air may be directly insufflated into a pulmonary vein, return to the left side of the heart, and probably travel to the brain, resulting in a cerebral air embolism (WEISS AND ROTH , 1994).

Boyle's law explains not only the pathophysiology of a gas embolism but also the rationale for treatment. Recompression in a hyperbaric chamber decreases the size of the bubble through a direct pressure effect; and the use of oxygen accelerates nitrogen washout, further decreasing the size of the bubble (WEISS AND ROTH , 1994).

HENRY'S LAW: States that the amount of an ideal gas that is physically dissolved in solution is directly proportional to the partial pressure of the gas ($C = n [P_g]$).

HBOT for acute and chronic stroke is based on Henry's Law which can be interpreted as follows: the amount of a gas, e.g. oxygen, that is dissolved in a liquid solution, e.g. blood, is proportional to the pressure of the gas interfacing with that solution. Since nearly 98-99% of hemoglobin in blood is saturated with oxygen at sea level all additional oxygen added by hyperbaric oxygen exposure is dissolved in the liquid plasma portion of the blood. It is this dissolved oxygen that exerts its drug effect on the pathology and pathophysiology in stroke and the other neuropathologies.

Another example of Henry's law at work is observed when large amounts of carbon dioxide are dissolved under pressure in soft drink bottles. When the cap is suddenly removed, the ambient pressure in the bottle is dramatically reduced. As a result, millions of microscopic bubbles come out of solution (WEISS AND ROTH , 1994).

This example is also applicable, when considering decompression sicknesses, in situations where a diver reaches extreme depths, spending extended periods of time or maybe ascending too quickly. As a result, nitrogen (in divers breathing compressed air) comes out of solution and bubbles form in the circulation and tissues. Henry's law also explains the rationale for treating decompression sickness in a hyperbaric chamber. Recompression in a hyperbaric chamber can re-dissolve the gas bubbles, allowing for a more controlled decompression (WEISS AND ROTH , 1994)

THERAPEUTIC EFFECTS OF HBO IN HUMANS

Physiologically, hyperoxia has a number of other effects. Hunt and others have demonstrated in a number of experimental models and clinical studies that elevated tissue wound oxygen tensions result in accelerated healing and more rapid resolution of infection (Jain KK, 1990).

Hyperoxygenation causes:

1. Increases angiogenesis, fibroblast proliferation, collagen formation, epithelialization, and the ability of white blood cells to kill bacteria.

periods of relative hypoxia are needed for maximal angiogenesis and stimulation of fibroblasts and macrophages (Hart GB, 1971). Neo-vascularization in hypoxic areas by augmenting fibroblastic activity and capillary growth. This is useful in radiation tissue damage and other problem wounds.

2. Immune stimulation by restoring WBC function and enhancing their phagocytic capabilities and causes vasoconstriction. This may be beneficial in a patient with a crush injury and/or compartment syndrome. The vasoconstriction decreases edema and compartment pressures while hyperoxygenating endangered muscle tissue. (Holbach KH, Wassmann H, Hoheluchter KL, et al., 1977) **Vasoconstriction** reduces edema and tissue swelling while ensuring adequate Oxygen delivery and is thus useful in acute trauma wounds and burns.

3. Bactericidal for anaerobic organisms & inhibits growth of aerobic bacteria at pressures > 1.3 ATA. It Inhibits production of alpha-toxin by C Welchii and is synergistic with Aminoglycosides and Quinolones. Thus it is life saving in gas gangrene and severe necrotizing infections.

4. At very high oxygen tensions, oxygen has an antitoxin effect with respect to carbon monoxide, clostridial, exotoxin, and possibly cyanide hydrogen sulfide, and carbon tetrachloride. In addition to a general antibacterial effect, hyperoxia is especially effective with respect to anaerobic infections (Anderson DC, Bottini AG, Jagiella WM, et al. , 1991)

5. Reduces half-life of Carboxyhaemoglobin from 4 to 5 hours to 20 minutes or less and is the treatment of choice for Carbon Monoxide poisoning in fire victims.

6. Mechanical effects – direct benefit of increased pressure helps reduce bubble size in Air Embolism and Decompression Illnesses
7. Reactivates "sleeping cells" in the penumbra region around central dead neuronal tissue. This is the basis of its use in neurological conditions. It also reduces adherence of WBCs to capillary walls and maybe useful in acute brain and spinal cord injury.

BENEFICIAL EFFECTS OF HBO

- HBOT is safe accompanied by very few and minor side effects
- Addition of HBO obviates the need for frequent surgical procedures → promotes healing and early mobilization of the patient.
- Reduces length of hospitalization and thereby overall treatment and rehabilitation costs.
- Emerging role in indications which have lifetime disabilities

ADVERS EFFECTS/ COMPLICATIONS

Hyperbaric oxygen therapy is safe when used in standard protocols. One of the most common side effects may be slight pain in the ears (aural barotraumas) due to a blocked Eustachian tube. Less commonly, pneumothorax and air embolism and transient reversible myopia after

prolonged HBO therapy is experienced. An occasional patient may be claustrophobic. Fire is a realistic hazard but preventable by strict safety procedures (Edmonds C, Lowry C, Pennefather J, 1994), (Brenk, 1970).

Organ	Pathology	Presentation
Sinuses	Congestion and/or occlusion	Pain, bloody discharge
Middle ear	Eustachian tube occluded Failure to equalize pressure within middle ear space	Edema, rupture, or retraction of tympanic membrane Hemorrhage
External ear	Wax build-up or ear plugs occlude canal	Pain, bleeding
Inner ear	Oval or round window rupture	Ataxia, vertigo, tinnitus, hearing loss
GI tract	Gas in bowels, distention on ascent	Vomiting, nausea, flatulence, colicky pain
Teeth	Infected or restored teeth (may harbor gas)	Tooth pain Tooth implosion or explosion
Gas embolus	Emergent decompression with blocked glottis (extremely rare)	Sudden decreased level of consciousness; hemiplegia, blown pupil

TABLE 3 ORGANS affected by barotraumas (UNDERSEA AND HYPERBARIC MEDICAL SOCIETY, 1999)

INDICATIONS FOR HYPERBARIC OXYGEN THERAPY

A. UNIVERSALLY ACCEPTED:

These indications are supported with peer reviewed proof of efficacy

Wounds:

- Problem, non-healing wounds and ulcers (diabetic, venous etc)
- Infective wounds - gas gangrene, refractory osteomyelitis, Necrotizing soft tissue infections
- Acute traumatic ischemias, crush injuries, compartment syndromes
- Compromised skin grafts and flaps
- Thermal burns

Oncology:

- Late radiation induced tissue damage and complications due to endarteritis
- Prophylactically adjunctive to therapeutic radiation, for preparation of surgery or implant procedures in previously irradiated fields

Primary Line of Treatment:

- Air or gas embolism
- Decompression Sickness
- Carbon Monoxide poisoning, smoke inhalation

Other Indications

- Acute Sensorineural Hearing Loss
- Intracranial Abscesses
- Bell's Palsy

B. RESEARCH INDICATIONS:

Role of HBOT in these indications is being studied in international trials

- ❖ HBOT in neurological illnesses – cerebral palsy, stroke, head injury
- ❖ HBOT as a radiosensitiser in Glioblastoma multiform and re-irradiation of sqamous cell Ca

A detailed elaboration of all indications a beyond this publication for further information see (Undersea and Hyperbaric Medical Society, 1999).

INDICATIONS FOR HBOT IN NEUROLOGICAL ILLNESSES

Cerebrovascular accidents (stroke): The reported rate of improvement is 40% to 100%, which is much higher than the natural rate of recovery. It shows a striking reduction in spasticity possibly due to improved function of neurons in affected areas or the brain and secondly to rise of PO2 in the spastic inactive and hypoxic muscle. Additionally there is an improvement in the cognitive and mental performance. The major criticism is that none of the reported studies are random controlled.

Acute traumatic brain injuries: HBO causes reduction of CBF thus reducing intracranial tension yet providing concomitant high doses of Oxygen to the brain. It interrupts the cycle of Ischemia, Hypoxia, edema and enzymatic derangements. There is improved aerobic metabolism, reduction in lactate levels, increase in creatinine phosphate and ATP levels. Elevation of partial pressure of Oxygen increases the diffusion distance, and O2 delivery in

abnormal areas is enhanced. However there has to be a responsive cerebral circulation. It is contraindicated when a stage of vasomotor paralysis has developed, and must not have fixed and dilated pupils. Most favorable results are obtained in patients in mid level Glasgow Coma scales.

Spinal cord injury: There is evidence that it is useful in Spinal cord traumas especially if administered within the first 4 hours and for subsequent rehabilitation of Spinal damage patients.

Cerebral Palsy: Evidence now shows that HBO therapy may dramatically improve some CP symptoms – spasticity, vision, hearing, and speech. However improvement, if any, will vary from patient to patient. More oxygen may help many children with cerebral palsy, but it is NOT a cure. It is simply a way of ensuring the most complete recovery possible and must be combined with other therapies.

Bell's palsy: Steroids and surgical decompression are the only treatment used currently but results are inconclusive as to their benefit. HBO added to other treatment increases the efficacy of the treatment and reduces the period needed for restoration of complete function of the damaged nerve.

CONTRAINDICATIONS TO HYPERBARIC OXYGEN

Condition	Rationale
Claustrophobia	Anxiety
Pneumothorax	Gas emboli, pneumomediastinum Pneumoperitoneum Tension (pneumothorax), Subcutaneous emphysema
History of spontaneous pneumothorax	Increased lung bleb incidence (pneumothorax)
Chronic obstructive pulmonary disease	Increased oxygen intolerance Increased risk of seizures
Pneumocystic carinii pneumonia	Questionable fetal teratogen
Seizure disorders	Barotrauma to sinus/ear/lung
Pregnancy*	Decreased threshold for oxygen-induced seizures
Upper respiratory infection	Increased hemolysis
Hyperthermia	
Hereditar spherocytosis	
Optic neuritis	Questionable - Increased optic nerve pathology
Malignant tumors	Questionable - Increased vascularity for tumors

Acidosis	Decreased threshold for oxygen seizures
Drugs	
cis-platinum	Decreased wound healing
Doxorubicin	Increased free oxygen radicals
Bleomycin	Pulmonary fibrosis leading to pneumothorax
	Decreased threshold for oxygen seizure
Steroids	Dehydration (increased risk of decompression sickness)
Alcohol	Spontaneous combustion
Aromatic hydrocarbons	Inhibits superoxide dismutase
Disulfiram	Decreased seizure threshold
Nicotine	

TABULKA 3 CONTRAINDICATIONS (UNDERSEA AND HYPERBARIC MEDICAL SOCIETY, 1999)

*HBO may be required in pregnancy in situations of carbon monoxide poisoning, cerebral gas embolus, decompression sickness, or clostridial myonecrosis.

METHODOLOGY

ADVISORY GROUP

Technical experts where identified to assist in formulating the research questions and identifying relevant databases for the literature search. This included a research supervisor, neurologist specializing in stroke, a physician with an HBOT practice, a neuro-researcher from the academy of sciences. Throughout the project period, we consulted individual members of the expert advisory group (AG) on issues that arose in the course of identifying and reviewing the literature.

SCOPE AND KEY QUESTIONS

This review addresses the following questions:

Which part does HBOT play in the regeneration of damaged tissues after acute ischemic stroke?

What is the relationship between HBOT and synaptogenasis in patients after stroke?

In which way does HBOT work to improve spasticity (a muscle disorder common in patients after stroke)?

To identify the patient groups, interventions, and outcomes that should be included in the review, we read back ground material from diverse sources including textbooks, scientific meeting proceedings, and Web sites. We also conducted focus group and interviews to improve our understanding of the clinical logic underlying the rationale for the use of HBOT. In the focus group, we identified outcomes of treatment with HBOT that are important to patients and examined whether patients, who have experience with HBOT value certain outcomes differently. A broader goal of the focus was to better understand the main pathophysiologic reactions that brain cells undergo during ischemic brain attack. By reviewing the fundamentals of stroke we aim to achieve a clear view on the subject in order to recognize the therapeutic specificity that hyperbaric oxygen therapy (HBOT) offers. We also took a closer look on the basics of HBO, its history, physiological aspects, indications, the principals that accompany it.

CRITERIA FOR CHOSING HYPOTHETIC FOCUS GROUP

1. Intervention:
    - ❖ Hyperbaric Oxygen Therapy: any treatment using 100 percent oxygen supplied to a patient inside a hyperbaric chamber that

is pressurized to greater than 1 atm; any frequency, duration, and total number of treatments.

2. Population:
   - ❖ Patients with thrombotic stroke, excluding patients with transient ischemic attack (TIA), hemorrhage (e.g., subarachnoid hemorrhage), or vasospasm.
   - ❖ Patients with progressive neurologic diseases (i.e., multiple sclerosis, Parkinson's disease, Alzheimer's disease, and chronic cerebral insufficiency), acute infectious processes (i.e., mucormycosis), radiation sensitization of brain tumors, and reports of treating eye damage or sudden deafness were excluded.
   - ❖ The use of HBOT for approved indications such as acute carbon monoxide poisoning or acute air embolism was also excluded.

OUTCOMES

Articles reporting clinical end points where soughted. We focused on HBOT mechanism of action in relation to the pathophysiologic reactions of brain cells after ischemic stroke. In addition to that we also focused on the health outcomes, including mortality and functional changes. In reviewing articles for inclusion in this report, we were particularly interested in studies that reported both intermediate measures (physiologic measures, such as intracranial pressure, changes in cerebral blood flow or results of imaging studies) and health outcomes, to analyses the effective evidence HBOT. Hence, we included studies that reported the effect of HBOT on elevated intracranial pressure, an intermediate outcome that is currently a main determinant of treatment in current clinical practice.

DESIGN

- We included studies of both animals and human subjects that reported original data
- We used the algorithm in Chart 1 to classify the design of studies. All of the study designs in the figure were included in the review except for non-comparative studies (e.g., case reports).
- Before-after or time-series studies with no control group were included.

LITERATURE SEARCH STRATEGY

We searched a broad range of databases to identify published and unpublished studies of the effectiveness and harms of HBOT in patients with stroke. Each database initially was searched from its starting date to November 2007.

The Databases We Searched Were:

MEDLINE

- Premed LINE

EMBASE

- CINAHL (Cumulative Index to Nursing & Allied Health)
- Cochrane Database of Systematic Reviews
- DARE (Database of Abstracts of Reviews of Effectiveness)
- MANTIS (Manual, Alternative and Natural Therapy)
- Health Technology Assessment Database
- The Undersea & Hyperbaric Medical Society: a large bibliographic database (30,000 records), http://www.uhms.org/library.htm
- The Database of Randomized Controlled Trials In Hyperbaric Medicine, http://hboevidence.com/
- European Underwater and Baromedical Society, http://www.eubs.org/
- International Congress on Hyperbaric Medicine, http://www.ichm.net/

Hand Searches: The references of all included papers were hand searched. In addition, independently conducted hand searches of the references from the *Acute ischemic stroke and imaging,* (Aneesh B. Singhal, Eng H. Lo,Turgay Dalkara, Michael A.Moskowitz, 2006) *Textbook of Hyperbaric Medicine* (Jain K, 1999) Merck-manuale of medicin (Mark H. Beers, 2003).

Update literature searching of the electronic databases MEDLINE, PreMEDLINE, EMBASE, CINAHL, the Cochrane Library, and the Health Technology Assessment Database was completed on August 2007, using the same search strategy as used for the initial searches. Finally, a supplemental search of MEDLINE, PreMEDLINE, and EMBASE was conducted in October 2007.

ASSESSMENT OF PAPERS FOR ELIGIBILITY

A reviewer (TJ) independently assessed each title and abstract located through the literature searches for relevance to the review, based on the intervention, population, outcome, and study design criteria listed above. Due to time constraints, only studies originally published in the English language were considered for review. Retrieved where full- text article, report, or meeting abstract of all citations that met the eligibility criteria. Independently, the eligibility criteria where reapplied to these materials.

DATA EXTRACTION

Extraction of data from studies was performed by the reviewer. Each study was assessed for quality using predetermined criteria. An overall assessment of each body of literature was made based on the internal and external validity, and consistency and coherence of the results of studies.

ASSESSMENT OF STUDY VALIDITY

All trials were assessed using a list of items indicating components of internal validity in a standardized fashion, based on validity checklists developed at the National Health Service Centre for Reviews and Dissemination and by the US Preventive Services Task Force (Dissemination, 2001).

Internal validity: Indicates the level of confidence we have in the accuracy (validity) and reliability (or reproducibility) of the results of the study. The internal validity of a study is assessed based on criteria set for a specific study design. In this way, an observational study would not be judged by criteria for randomized controlled trials (RCTs), but rather by criteria that apply to—and can be met by—a good-quality observational study. For RCTs and nonrandomized controlled trials, the items assessed for internal validity were randomization/allocation concealment (e.g., randomization and concealment procedures, stratification), baseline comparability of groups, timing of baseline measures, intervention, outcome measures, timing of follow-up measurements (long enough to assess effects), loss to follow-up, handling of dropouts or missing data, masking, statistical analysis (if any), and general reviewer comments. The rationale for selecting these criteria is as follows:

- **Methods used to ensure comparable groups at baseline.**

Some methods of allocating subjects to treatment and control groups are more likely to prevent bias and to result in groups that are comparable at

baseline. Randomization, the best method to allocate patients to groups, is most effective if it is *concealed.*

❖ **Baseline comparability of groups.**

The purpose of randomization is to distribute prognostic characteristics equally in the treatment and control groups. Effective randomization distributes known as well as unknown prognostic factors in an unbiased manner. We judged studies on how thoroughly they reported baseline characteristics known to affect prognosis and on whether there were baseline differences between the groups. When the method used to conceal allocation is inadequate or is not described, such differences may suggest that randomization was subverted or carried out incorrectly.

❖ **Use of validated outcome measures.**

The use of validated, reliable outcome measures prevents based on the part of persons who assess outcomes. The use of measures that have not been shown to be valid and reliable reduces confidence that the findings are accurate.

❖ **Masking of outcome assessment.**

The investigators who judge whether the patients have improved should not be aware of which patients received the treatment. This benefit of the treatment can influence an observer's assessment of a patient's condition.

❖ **Stable baseline.**

A before-after treatment study or a time series study relies on the premise that the results after treatment are better than could be expected with standard medical care and the passing of time. For a reader to accept this premise, the study must describe thoroughly the baseline condition of the patients, other aspects of care management, the degree of social support, and any other factor that might predict the outcome. The baseline condition of

the patients must be established to be stable; otherwise, changes seen cannot be distinguished from an evolving clinical picture. Omission of even one characteristic that could have accounted for the results raises doubt about whether it was really the treatment that is responsible. The baseline assessments should be timed in a manner that is appropriate to the study's circumstances.

❖ **Use of valid outcome measures and masking of outcome assessment.**

Each study was assigned an overall rating (good, fair or poor) according to the US Preventive Services Task Force methods. The definitions of the three rating categories for these types of studies are as follows.

Good: Comparable groups assembled initially (adequate randomization and concealment, and potential confounders distributed equally among groups) and maintained throughout the study; follow up at least 80 percent; reliable and valid measurement instruments applied equally to the groups; outcome assessment masked; interventions defined clearly; all important outcomes considered; appropriate attention to confounders in analysis; for RCTs, intention-to-treat analysis.

Fair: Generally comparable groups assembled initially (inadequate or unstated randomization and concealment methods) but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments acceptable (although not the best) and generally applied equally; outcome assessment masked; some, but not all important outcomes considered; appropriate attention to some, but not all potential confounders; for RCTs, intention-to-treat analysis.

Poor: Groups assembled initially not close to being comparable or not maintained throughout the study; measurement instruments unreliable or invalid or not applied equally among groups; outcome assessment not

masked; key confounders given little or no attention, for RCTs, no intention-to-treat analysis.

The discussion of results and conclusions in this report is based on the analysis of information extracted from the above mentioned text books as well as good- and fair-quality studies. Results of good-quality studies have a high likelihood of being both valid and reliable. Fair-quality studies have important but not fatal flaws in their design or conduct. The category of fair is broad, with some studies that are probably valid and others that are unlikely to be valid, depending on the specific flaws found and their severity. The inadequacies found in poor-quality studies make the results unreliable.

External validity: External validity refers to the applicability of the results of the study to clinical practice.

I. The investigators should describe the criteria used to identify eligible subjects for the study.
II. They should report the numbers of patients who were considered for inclusion in the study, the number that met the eligibility criteria, and the number that actually entered the study.
III. They should report the age range, the severity of disease or disability, the prevalence of comorbid conditions, and other sample characteristics that would enable a clinician to assess the applicability of the results to the patient population for which the intervention is intended.

EVIDENCE

The analyses of individual studies reviewed for quality and consistent evidence for each key question is based on the internal and external validity. An analysis of whether the body of evidence is sufficient to provide a clear answer to the key questions was undertaken.

SYNTHESIS OF RESULTS

Results of data extraction and assessment of study validity are presented bellow as a narrative description.

Studies used: The literature searches, both electronic and by hand, identified over 600 references relating to HBOT and brain injury, pathophysiologic reactions of brain cells after ischemic stroke and stroke as a whole. These references/abstracts were assessed against the inclusion criteria and 100 full papers where obtained. Upon examination of the full papers, 40 were excluded, because they did not meet the inclusion criteria. Sixty studies focused more on traumatic brain injury and cerebral palsy and had no reports of ischemic stroke among them were also animal studies, and the rest were irretrievable. In total 34 studies met inclusion criteria (5 controlled trials, 17 observational studies and 12 abstract only/conference proceeding) most of which are used throughout this report.

The review of studies leads to the conclusion that HBOT is beneficial in acute global ischemic/anoxia regardless of treating pressure, frequency, duration, number of treatments or time to onset of HBOT post insult. The best available evidence found shows benefit from HBOT for stroke. Most observational studies reported good, and sometimes dramatic, results. Therefore, conclusions about the effectiveness of HBOT for stroke can be drawn from this body of evidence.

Human clinical studies: The human HBOT experience in cerebral ischemia is extensive, complicated and spread across multiple medical conditions. Despite the heterogeneous group of studies, the data shows a beneficial effect of HBOT, especially in the large series. Five controlled trials examined the effect of HBOT in patients with stroke. Four of these were randomized (Nighoghossian N, Trouillas P, Adeleine P,et al., 1995) (Anderson DC, Bottini AG, Jagiella WM, et al. , 1991) (Sarno JE, Rusk HA, Diller L, et al. , 1972) (Sarno MT, Sarno JE, Diller L. , v) (Rusyniak DE, Kirk MA, May JD, et al. , 2003). One study was non-randomized (Marroni.A, 1987). The number of patients ranged from 32 to 80. Strokes were described as ischemic, (Nighoghossian N, Trouillas P, Adeleine P,et al., 1995), (Sarno JE, Rusk HA, Diller L, et al. , 1972), (Rusyniak DE, Kirk MA, May JD, et al. , 2003) thrombotic, (Marroni.A, 1987) or vascular. (Sarno MT, Sarno JE, Diller L.) Two trials included only acute patients who were within 24 hours of the onset of their stroke, another enrolled patients within 2 weeks of onset another enrolled only patients who were at least 2 months past their stroke (range 2 to 172 months, average 29.2 months) and were no longer receiving any therapy or rehabilitation, and the last included patients at least 3 months post-stroke (range 3-108 months). HBOT protocols varied. The dose was either 1.5 to 2.5 atm, and there was significant variation in the number and duration of treatments. The duration of each session ranged from 40 to 60 minutes, and the number of treatments ranged from a single session to 30. Monoplaced chambers were used in three studies

and multiplaced chambers in two studies. Control groups were active in the randomized controlled trials; three matched the pressure of the treatment group but used room air instead of 100 percent oxygen and one used 100 percent oxygen with 1.14 atm pressure. One added occupational and physical therapy to the regimen in both control and treatment group patients. The non-randomized controlled trial assigned 80 stroke patients to eight comparison groups with combinations of in-water or "dry" physical therapy; HBOT at different doses (1.5 or 2.0 atm); both HBOT and physical therapy; or no treatment. Patients were assigned to treatment group based on which group had an open position at the time they were assigned. In two of the randomized trials, both patients and examiners were masked to treatment assignment. In the other two, the title describes the study as double-blind, but there is no mention in the text about masking of outcome assessors (the patients received sham treatments). In the non-randomized controlled trial, the examiner, but not the patient, was masked to treatment assignment. One study reported outcomes only immediately following a single HBOT treatment, two measured outcomes at various points over 1 year, and two followed patients for 3 months.

Randomized controlled trial, **Nighoghossian, Trouillas, et al. (1995),** (Nighoghossian N, Trouillas P, Adeleine P,et al., 1995) enrolled 34 patients within 24 hours of the onset of their stroke. Twenty-seven (79 percent) patients completed the study. When the mean neurological scores of the groups were compared, patients who received 10 HBOT treatments had significantly higher scores at 12 months on two of the three scales used (Orgogozo scale and Trouillas scale) compared to patients who were assigned to the control group.

Controlled study, **Marroni et al. (1987),** was a non-randomized trial that used eight different treatment regimens combining HBOT with in-water or dry physical therapy compared to no treatment or in-water physical therapy alone (no HBOT) (Marroni.A, 1987) The number of patients in each

treatment group ranged from 7 to 12; all were stable and were no longer receiving any therapy or rehabilitation. Mean outcome measure scores were plotted for each group. After 60 days, the groups of patients treated with HBOT improved by 1 and 1.8 degrees on the Kurtzke functional scale (a scale measuring walking ability and other abilities in patients with multiple sclerosis), while control groups had no improvement. Groups receiving HBOT plus physical therapy improved more, and the in-water HBOT group achieved the largest improvement. Patients were also evaluated on the Neuromotor Disabilities Evaluation Scale. This invalidated scale, developed by the study authors, measures 10 groups of limb and system function (e.g., finger and hand function, muscular strength, walking ability) on a scale ranging from 17 (best) to 111 (worst). Over a 3-month evaluation period, mean scores in the dry HBOT groups improved by 3.1 to 3.8 degrees, and patients in control groups improved 1 degree. There were no differences among these groups based on concurrent physical therapy or HBOT dose (1.5 or 2.0 atm). The groups receiving HBOT and concurrent in- water physical therapy improved by 7.7 degrees (1.5 atm) and 11.6 degrees (2.0 atm).

There are 17 observational studies of HBOT in patients with stroke. Nine of these are before-after studies, (Y.Imai, 1974) (Shn-rong, 1995), (Heyman A, Saltzman HA, Whalen RE. , 1966) (KK., 1989) (W-R., March 1-4, 1987,) (Noguchi T, Itoh N, Aoyagi M, et al., 1983) (D.Steenblock, 1998; Tsuro M, Nakagaway Y, Kitaoika K, et al., 1983; Neubauer RA, End E, 1980)seven are time series that measured outcomes at several points before and after treatment, (Hart GB, 1971) (Holbach KH, Wassmann H, Hoheluchter KL, et al., 1977) (Holbach KH, Wassmann H, Bonatelli AP. , 1977.) (Jain KK, 1990) (JP., 1981) (Saltzman HA, Anderson B, Jr., Whalen RE, et al., 1965) (Wassmann H, 1986.), and one was a retrospective comparison of cohorts from two different hospitals (Pilotti L, 1991). The number of patients in these studies ranged from 18 to 490. HBOT treatment protocols were often

adjusted according to the patient's condition, so they were not standardized either within or between studies. In general, the usual dose was between 1.5 and 2.0 atm. Duration ranged from 30 to 90 minutes, with most reporting about 15 treatments, although there was a wide range. Two studies reported mortality rates; three measured grip strength with a dynamometer; one performed a mental status examination, two-point discrimination, and repetitive thumb/finger movements; two measured spasticity on a five-point scale; and one measured 33 different functions of cognition and motor ability. One study used a scoring system that included one standard test to measure memory (Bender-Gestalt Memory Test), but the other components of the score were not validated or well described. In three studies (Y.Imai, 1974), (Holbach KH, Wassmann H, Bonatelli AP. , 1977.) (Jain KK, 1990), outcomes were measured at the conclusion of HBOT treatment. Since the duration of treatment varied according to patient response, the timing of these follow-up measures also varied. Others followed up patients for 6 weeks, (Holbach KH, Wassmann H, Hoheluchter KL, et al., 1977) every 3 months for 1 year, (Jain KK, Klausenbach F, Fischer B., 1989 (June 6-11) at 6 and 12 months after treatment, (Shn-rong, 1995), and 4.5 years after treatment (D.Steenblock, 1998; Tsuro M, Nakagaway Y, Kitaoika K, et al., 1983; Neubauer RA, End E, 1980). As a group, the observational studies reported that between 20 and 83 percent of selected patients with stroke improved after HBOT therapy

Twelve studies of HBOT in stroke reported their results only in meeting abstracts. Two were controlled trials. Only one reported detailed inclusion criteria. One included subjects with other diagnoses in addition to stroke (chronic traumatic, hypoxic, and anoxic brain injuries) and did not report outcomes in stroke patients separately. One included mainly patients in critical condition in a coma. The number of patients ranged from 4 to 140. Doses ranged from 1.5 to 3.0 atm, duration from 40 to 90 minutes, and number of treatments from 1 to 80. Two studies did not report the HBOT

protocol used. One of the controlled trials used a Neurological Recovery Score (improvement at 12 months HBOT vs. control, p = 0.031); the other reported recurrent stroke or TIA (4.8 percent TIA in HBOT vs. 5.9 percent stroke in control, p not given). Two uncontrolled studies reported observations or results of unspecified neurological examinations. One stated that 100 percent of 18 patients with chronic traumatic, ischemic, hypoxic, and anoxic brain injuries showed motor, behavioral, personality or cognitive gains by 40 treatments. In another, 80 percent of 140 patients with ischemic stroke improved. The other did not report the proportion of patients who improved, but reported that "nearly all" patients who responded favorably to HBOT showed a positive response to extra- intracranial arterial bypass surgery. Other uncontrolled studies measured hand grip and spasticity143 (improvement in all four patients), recovery of consciousness (17 percent of six patients regained consciousness), and short-term memory quotient (memory quotient improved significantly from baseline, p < 0.001).

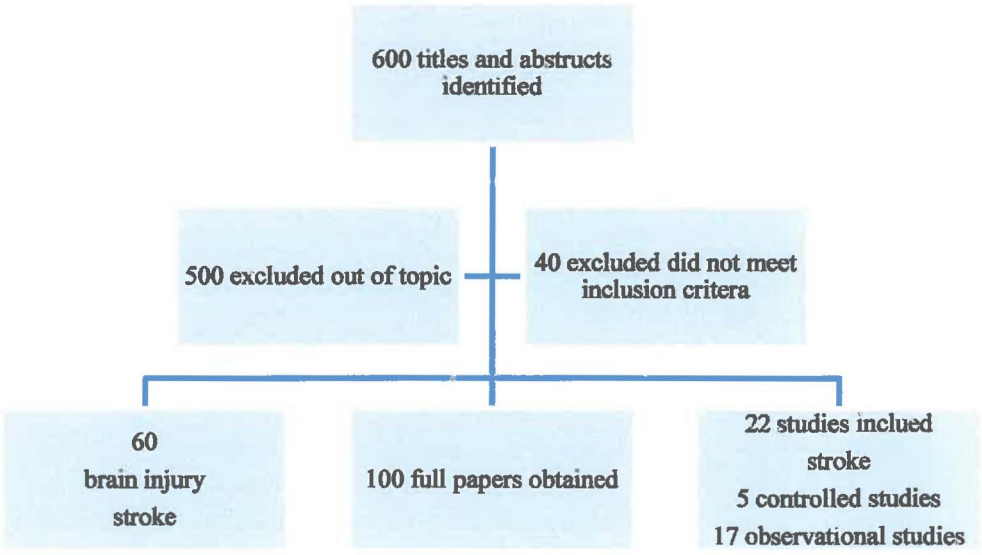


Chart 1 HBOT Literature Search Reuslt

DISCUSSION

In this section an analysis of data as well as a detailed discussion will be undertaken.

The core and penumbra concept, can guide us in understanding patient management. According to (W.J.Koroshetz, R.G.González, 2006) the core is the irreversible necrotic region and the penumbra is the region of the brain surrounding the necrotic area (core) this area is underperfused and is in danger of infracting. Due to the fragile state of the penumbra, there might be a probability that early intensive (physically stressful) physical therapeutic intervention might lead to a progression of irreversibly damaged tissue in the penumbra, resulting in a deterioration of patient's state. It is also well known that in patients with cardiovascular diseases a blood supply that is adequate at rest may be inadequate when cardiac demands are increased by exercise or other forms of stress. Increase in stress triggers the release of stress hormones, excessive corticosteroids and catecholamines produced at these times affects the organism largely. Stress hormones have anti-angiogenic properties and accelerate the production of free radicals and lipid peroxidation in blood vessels, all of which will have a detrimental effect on newly forming and fragile capillaries. Hossmann 1994 supports this by his elaboration of the importance of decreasing metabolic work load in penumbra regions for the improvement of ischemic ressistance in stroke.
Increase in stress might also result in an overall increased in blood pressure. Hypertension according to (W.J.Koroshetz, R.G.González, 2006) is the most significant risk factor for stroke. He further elaborates that, „elevation in blood pressure plays a large role in the development of vascular diseases for example, cerebrovascular arteries as well as small vessel occlusion".

With this in mind, clinically important questions arise. An example may be, whether intensive (physically stressful) physical therapeutic intervention in acute periods leads to stroke risk factors? Other questions regarding optimal physical therapy, initiation time as well as frequency, however has only rarely or not been address from this point of view so far. Might undertaking light forms of physical therapy, several times a day and gradually increasing in intensity with at a constant frequency be the answer for the ultimate outcomes? Thus decreasing the probability of penumbra infarction and the resulting deterioration of patient's state?

Cerebral ischemia is among the most common pathophysiologic condition involving the central nervous system. It is understood as a result of a focal perfusion deficit in an area supplied by brain artery, which can be either reversible or permanent. The perfusion deficit is commonly a result of arterio-arteriolar or cardiac embolus or the thrombotic occlusion of a brain artery. Symptoms of ischemic stroke include hemiparesis, aphasia and visual impairments depending on the affected vascular territory (Dirngl U.1999).

An understanding of stroke pathophysiology is responsible for the major breakthroughs in developing new therapeutic strategies. Recently several trial assesing the usage of neuroprotective drugs, in stroke patients where undertaken without particular success. Despite this there is an ever growing availability of new promising therapeutic options. One such option is hyperbaric oxygen therapy. HBOT has been suggested as a neuroprotective adjuvant and/or therapeutic option for the treatment of acute focal cerebral ischemia (see section on HBOT).

Recently, great alternations with regards to the focal point of the pathophysiological changes during stroke have occurred. The shift is mainly from the earlier focus on blood flow and metabolism to the biochemical and cellular mechanisms of stroke pathophysiology. In addition to this, molecular and genetic aspects have also gained particular attention.

With this in mind it is clear that for a better understanding of the pathophysiology of focal cerebral ischemia, mechanisms such as cellular, molecular, circulatory as well as metabolic mechanisms should be put into greater consideration. This knowledge can lead to affective therapeutic strategies and possibly the prevention of focal cerebral ischemic consequences (Hossmann KA 1994).

For many years cerebral ischemia has been thought to release glutamate from the hypoxic, damaged cells and this glutamate was thought to potentiate and propagate the initial hypoxic damage. The recent explanation is also based on hypoxic glutamate-mediated injury, but caused by peri-infarct spreading depression-like depolarization. (Hossmann KA 1994) supports this concept. He states that glutamate-mediated injuries are caused by peri-infarct spreading depression-like depolarizations. These irregular depolarizations are thought to initiate or worsen hypoxic episodes and cause a further suppression in protein synthesis. These depolarization also initiate gradual deterioration in energy metabolism and a progression of irreversibly damaged tissue into the penumbra zone (see chapter no basic pathophysiology). Thus "interventions to improve ischemic resistance should therefore aim at improving the oxygen supply or reducing the metabolic work load the penumbra region."

Scientific evidence suggests that, a complex sequence of pathophysiological event occurs in stroke. These pathophysiologc events involve excitotoxicity, peri-infarct depoloarization, inflamation and programed cell death (see fig. 2). With this model at hand, it is apparent that focal cerebral ischaemic therapeutic strategies can be targeted to specific mechanisms that occur at specific points in time. Drugs such as glutamate receptor antagonists for instance, says (lalbeit), „should be given right after the initial symptoms, for its excitotoxic interfering character, where as other drugs such as those aimed at inflammation or apoptosis may have an extended time frame and a smaller overall effect".

The contributions of non-neuronal cells and in particular glial cells in stroke pathophysiology, regeneration and repair are increasingly becoming appreciated. Due to the fact that these contributions of glial cells have only recently come into focus, scientist's knowledge in this subject is patchy. Nevertheless, evidence suggests that glial cells are the major contributors to tissue damage and repair after focal cerebral ischemia (Dirngl U.1999).

A focal point that recently captured the minds of researchers in the field of cerebral ischemia is the concept that elaborates endogenous neuroprotective mechanisms (see Fig.2). This concept describes the final infarct as a result of a „struggle" between protection and destruction. Several experiments on animals have been conducted with the aim of further elaborating these endogenous protective signaling cascades. The results indicated positive outcomes, particularly the protection of the brain against stroke by boosting these neuroprotective mechanisms (Dirngl U.1999). The first clinical trials aiming at the induction of primarily endogenous neuroprotection (e.g. erythropoeitin) are in progress.

In general when venturing into brain physiology and pathophysiology a very close interaction between neuronal and non-neuronal elements is observed. (Dirngl1999), states that, „stroke results in the infarction of brain tissue, called pannecrosis, (the death of all cellular elements in a given tissue volume) ". It is therefore important to understand, the role that all neuronal and non-neuronal cells (especially glial cells) play in the destructive as well as protective cascades, evolving in focally ischemic or reperfused brain (see table 7).

Scientific results show that ischemic penumbra is a dynamic process of impaired perfusion and metabolism. This impairment may eventually propagate with time from the center of ischemia to neighboring tissues. Enhancing blood flow to these areas resulted in the prevention of the spread

of cerebral infarction (Heiss, WD, Graf, R 1994). This could help in selecting the appropriate therapeutic interventions in patient after stroke.

Evidence indicates a reduction in the number of perfused capillaries in the penumbra. This loss of capillary perfusion is probably the result of a combination of changes that occur in the terminal capillary bed in acute ischemic processes. Due to the constrictive and restrictive changes, created by the ischemic process, red blood cells are no longer able to pass though ischemic and post-ischemic capillaries. Plasma, on the other has been shown to reach all ischemic and post-ischemic capillaries, and is able to pass through these capillaries (Hossmann 1993). HBOT makes use of this advantage that blood plasma offers. One of the mechanisms of action of hyperbaric oxygen is to increase the oxygen solubility in blood plasma. It is possible to dissolve sufficient oxygen (i.e. 6 vol% in plasma) to meet the oxygen needs of the brain (K.K. Jain, 1996). Therefore in the acute stroke patient, the use of hyperbaric oxygen is able to provide oxygen to ischemic neurons and to keep them alive while either endogenous or exogenous fibrinolytic mechanisms are brought to bear on the cerebral thrombosis that is causing the ischemia. This results in the salvage of the ischemic penumbra to a degree impossible with any other therapy.

Literature and clinical experience predicts that between 80 to 90 percent of stroke patients will be helped by hyperbaric oxygen. Injury to the brain causes blood vessels to be damaged or destroyed. The tissue that surrounds the area of outright necrosis has had its circulation compromised and may be only receiving a fraction of the blood flow and oxygen that it needs for optimum health. Thus a disruption in structure creates immediately a change (decrease) in function. This decrease in function remains for months or years and the neurons in these areas are said to be in "hibernation" or "sleeping". Hyperbaric oxygen treatments when given daily stimulate a process called

angiogenesis. New blood vessels form in the vicinity of the damaged tissues as a result of certain chemical signals (e.g. angiogenin) that are produced by the newly re-energized neurons, endothelial cells and macrophages and are then secreted into the surrounding tissues. These signals stimulate new blood vessels which slowly reconnect to the damaged tissues and within 60 days of daily treatments, the "sleeping" neurons wake up and resume their normal functions as the proper structures return back in place. The hyperbaric oxygen induced blood vessel repair results in a permanent structural change in the blood vessels that re-supply the previously damaged and nonfunctioning nerve tissue which was occurring due to diminished and inadequate blood flow. These new blood vessels improve the blood flow and oxygen delivery to the damaged brain tissues. This results in permanent improvements of stroke. Clinically, what you see is the return to life of a previously paralyzed and useless limb or limbs, improvement in swallowing, speech, thinking (cognition), memory, etc. Quite obviously not all of the disabilities disappear since there was a central core of dead tissue that cannot be revived. However, after the two months of therapy, these people may continue to improve for at least two years after their treatment with hyperbaric oxygen especially if they continue with physical therapy. This also occurs in patients with chronic ischemic stroke and may have not seen any improvement in their conditions for years after their stroke even with the use of any and all other therapies. (Davis 1994) refers to this as an indication that the brain's milieu intérieur in such cases are altered for the better since the neurons are able to slowly re-establish their lost connections in ways not possible before hyperbaric oxygen.

Comparative functional volume obtained by single photon emission computerized tomography (SPECT) often indicates a large region of recoverable tissue. This functional volume of the infarct size can be demonstrated to decrease after one to several hyperbaric oxygen treatments

(Neubauer, 1990, 1992). The increase in blood flow to the area of infarction that occurs as a result of hyperbaric oxygen can serve as a clinical test to determine if there are salvageable neurons still present in the penumbra. Presumably, if the test (SPECT first, then HBO then repeat SPECT) is positive, the person should receive benefit from the use of a series of hyperbaric oxygen treatments because of the revitalization of the ischemic penumbral tissues.

Following acute, localized lesions of the central nervous system, arising from any cause, there are immediate depressions of neuronal synaptic functions in other areas of the central nervous system remote from the lesion. These remote effects result from "de-afferentation", a phenomenon known as "diaschisis"(Neubauer, 1990).

After an interval of time, which will vary directly with the severity of the lesion, functional recovery may occur to some degree due to synaptic reactivation of neurons. This is favorably influenced by rehabilitation. Diaschisis most commonly manifests itself by such neurological signs as impaired consciousness or cognitive impairments including dementia, dyspraxia, dystaxia, dysphasia, incoordination and sensory neglect. The nature of diaschisis has been demonstrated by widespread depressions of local cerebral blood flow and metabolism extending far beyond the anatomical lesion. Neubauer pointed out that development of diaschisis is enhanced by latent circulatory disorders in both the affected and unaffected areas of the brain. Recovery of function is associated with recovery of local perfusion and metabolism (Neubauer, 1990).

Thus if functionless ischemic penumbral tissue can be "re-activated" and be made to function again, a corresponding amount of the areas of diaschisis will be returned to normal with normal blood flow and function returning.

Personal experience gained from observing a patient Mr. F.Ch. indicated vast improvements. Mr. F. Ch. underwent 22 sessions of hyperbaric oxygen therapy in a multiplaced hyperbaric oxygen chamber. His first session took place on the third day after his first stroke symptoms. We closely observed the development of his health status. It showed a striking reduction in spasticity, possibly due to improved function of neurons in the affected areas of the brain and increase of PO2 in the spastic, inactive and hypoxic muscle. In addition, clinically, we observed the return to life of previously paralyzed and useless limbs, improvement in swallowing, speech, thinking (cognition) and memory. We also observed great improvements in his mood and in his motivation. There was an overall improvement in his motor as well as psychological functions.

In this review, we sought to analyze the effect of HBOT in acute ischemic stroke by answering the question: the overall benefits regarding hyperbaric oxygen therapy after acute ischemic stroke.

Which part does HBOT play in the regeneration of damaged tissues after acute ischemic stroke?

The ischemic penumbra does not receiving enough blood flow. As a result, the tissues in this area do not get enough oxygen to function but do receive enough to stay alive. They are side to be, "sleeping neurons". These neurons are non-functional but anatomically intact and can be revived. In the acute phase of stroke, damaged, dying and dead brain cells develop leaky plasma membranes allowing calcium and sodium into these cells which is followed by the accumulation of water which produces extensive and damaging edema. This swelling, if severe, may kill the person within the first 24 to 72 hours. If the person does not die, it may take up to 9 to 12 months for the edema to resolve during which time the swelling compresses the involved brain blood vessels, limiting the flow of blood to the damaged tissues. As the swelling goes away, some of the blood vessels will regain their original diameters and normal blood flow will resume but other vessels will remain permanently narrowed, spastic or obliterated. HBOT has been shown to be effective at reducing the amount of edematous tissue of the brain significantly (see section on HBOT). The outermost portions of the ischemic penumbra (those portions closest to normal brain tissue) are able to metabolize but at a reduced rate compared to normal tissues; however, they are receiving

more blood and oxygen than the centrally located ischemic tissues. Adeno-sine, a metabolite of ATP, is released from ischemic core, when cells metabolise and repair. Adeno-sine is a vasodilator that stimulates new capillaries to grow into the ischemic penumbra (neovascularization). During the first year after a stroke, new blood vessels have been shown to be stimulated to move into the ischemic penumbra to re-supply it with a new blood supply (Anderson DC, Bottini AG, Jagiella WM, et al. , 1991).

Hyperbaric oxygen works to improve acute as well as chronic stroke patients by regenerating, repairing and generating new blood vessels to the injured parts of the brain. In the ischemic penumbra, the blood vessels are often constricted to the point that red blood cells cannot pass through them. This creates the situation where only plasma is able to pass slowly to part or most of the ischemic area. Since plasma has nutrients, the tissues of the ischemic penumbra are able to remain alive by using anaerobic glycolysis (metabolism without oxygen) also known as fermentation. Anaerobic glycolysis only produces 2 moles of ATP per mole of glucose metabolized instead of the 36 moles of ATP formed when oxygen is present. Thus the tissues suffer from a chronic shortage of ATP and its subsequent metabolite, adenosine.

Hyperbaric oxygen forces oxygen into the plasma to such a degree that as the plasma passes into the ischemic penumbra, the ischemic tissue begins to receive enough oxygen for aerobic glycolysis (metabolism that uses oxygen) to occur once more. This creates a surge of ATP production in the ischemic tissue which continues to be produced as long as the patient is within the hyperbaric oxygen chamber. When a patient is taken out of the chamber, blood oxygen and tissue oxygen levels fall back to pre-treatment levels of oxygen within 4 hours. As the tissue oxygen level falls, the newly generated ATP is used by the ischemic tissues and adenosine is released into the surrounding tissues in an effort by the tissues to continue receiving oxygen. As a part of this survival mechanism, adenosine and other chemical mediators are released into the surrounding tissues stimulating neovascularization. Done daily over

many days, the HBO stimulates new blood vessels to grow into the ischemic tissues returning them back to normal in terms of their oxygen supply. Recovery of function is associated with recovery of local perfusion and metabolism

What is the relationship between HBOT and synaptogenasis in patients after stroke?

The rationale of use of Hyperbaric Oxygen in neurological indications is based on the finding in SPECT studies that around the central area of neuronal death is the penumbra: peri-infarct zone having idling or sleeping neurons and gliosis (dead neurons) on CT scans may actually be viable tissue for years following the insult. HBO delivers high Oxygen to these "sleeping cells" and reactivates them.

This is achieved by reducing cerebral edema, reverses the reduced flexibility of erythrocytes and improves the function of neurons rendered inactive by ischemia/hypoxia. The improvement of brain function is reflected by the improved electrical activity of the brain."

Once the ischemic penumbral tissues are no longer suffering from a lack of oxygen, they are able to begin to repair their injured neurons, glial cells and extracellular matrix. These neurons repair their cell bodies, dendrites, axons and synapses. They also grow out and extend to the many lost connections that occurred at the time of the stroke. Due to these events, patients experience positive results during the 60 days of daily hyperbaric oxygen because of the renewed oxygen supply (neovascularization). In addition, most patients continue to see improvements for another six or more month after the completion of the course of hyperbaric oxygen due to continuing cellular repair and reconnections.

In which way does HBOT work to improve spasticity (a muscle disorder common in patients after stroke)?

Myelin sheaths cover many nerve fibers in the central and peripheral nervous system; they accelerate axonal transmission of neural impulses. Disorders that affect myelin interrupt nerve transmission.

Demyelination is often secondary to ischemic disorders, which can be segmental or patchy, affecting multiple areas simultaneously or sequentially. Extensive myelin loss is usually followed by axonal degeneration and often cell body degeneration; both may be irreversible.

Spasticity may be due to the following:

- Decreased function of neurons in affected areas or brain
- Decreased PO_2 in hypoxic and inactive muscles

Remyelination often occurs with repair, regeneration and complete recovery of neural function.

The possible mechanism of action offered by HBOT in neurological disorders is the relief of hypoxia, improved microcirculation and cerebral metabolism, reduced cerebral edema by vasoconstrictive effect, increased permeability of the blood-brain barrier and preservation of partially damaged tissue and prevention of further progression of secondary effects of cerebral lesions.

The hyperbaric oxygen induced blood vessel repair results in a permanent structural change in the blood vessels that re-supply the previously damaged and nonfunctioning nerve tissue which was occurring due to diminished and inadequate blood flow. These new blood vessels improve the blood flow and oxygen delivery to the damaged brain tissues. Due to an increase in oxygen delivery, damaged brain tissues are able to initiate reparation processers to their injured neurons, glial cells and extracellular matrix. Reparation of neural cell bodies, dentrites, axons, synapses as well as remyelinations occurs. This results in permanent improvements of neuron function.

The reported rate of improvement is 40% to 100%. It shows a striking reduction in spasticity possibly due to improved function of neurons in affected areas or the brain and secondly to rise of PO2 in the spastic inactive and hypoxic muscle. In addition clinically, what you see is the return to life of a previously paralyzed and useless limb or limbs, improvement in swallowing, speech, thinking (cognition), memory, etc. Quite obviously not all of the disabilities disappear since there was a central core of dead tissue that cannot be revived.

CONCLUSIONS

The present work shows the fundamentals of the use of HBOT in general. Davis (1994) in his work managed to show that literature and clinical experience predict that between 80% - 90% of stroke patients will positively benefit from HBOT. This is due to its beneficial effect. Some of this beneficial effects are, increase in oxygen delivery, decrease in cerebral edema, decreased lipid peroxidation, inhibition of leukocyte activation, maintenance of blood-brain barrier integrity as well as the reduction in the volume of brain infarction. HBOT is clearly not only useful for patients after acute ischemic stroke, but also for a variety of conditions indicated by UHMS (Undersea and Hyperbaric Medical Society, 1999).

This information is vital firstly because health care practitioners have tried a variety of different methods to improve the quality of daily life for post-stroke patients but the overall results where unsatisfactory. Although stroke is a leading cause of death and disability, its long term management is often marked by feelings of hopelessness on the part of both patients and professionals. Any treatment that provides increased functional abilities and helps these people live more independently and economically should be made available as soon as possible, for both humanitarian and economic reasons. Secondly because physiotherapy is a fast growing part of the medical field, in which more and more therapist are becoming independent. This independence requires accurate and effective decision-making skill, concerning patient care and management. In order to achieve these skills, it is imperative to consider the importance of understanding fundamentals, mechanisms of action and the effects of adjuvant therapies such us HBOT. Lastly, when considering clinical application of HBOT, potential benefits must be balanced against the potential toxicity. Hence, this work presents not

only the considered beneficial effects of HBOT; it also shows the adverse effects that may occur due to HBOT.

The reported rate of improvement is 40% – 100% which is much greater than the natural rate of recovery. In a number of both animal and human studies, hyperbaric oxygen has been shown to diminish cerebral blood flow from 1 to 29% (average 14.7%), which some people have claimed to be detrimental to a stroke or brain injured patient. All of these studies were done in normal non-brain injured subjects while the studies that were done in brain injured patients all showed an increase in cerebral blood flow (Jain, 1996 page 239).

Dr. K.K. Jain states that, "Vasoconstriction and reduced cerebral blood flow do not produce any clinically observable effects in a healthy adult when pressures of 1.5 to 2 ATA are used. The effects of HBO are more pronounced in hypoxic/ischemic states of the brain. HBOT reduces cerebral edema and improves the function of neurons rendered inactive by ischemia/hypoxia. The improvement of brain function is reflected by the improved electrical activity of the brain."

With this fundamental knowledge at hand, it is possible to continue from this cellular level to the next level. Evidence from well-conducted clinical studies is limited. Future work on this topic should aim to answer the arising question such as:

- The number of HBOT sessions recommented, before engaging physiothery as part of a complex healing intervention to patient after stoke?

A lack of agreement on the dosage of HBOT and duration of treatment was identified. Clear information on the dosage and duration of HBOT could be in an important research question to answer.

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SUPPLEMENTS

LIST OF SUPPLEMENTS:

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Žádost o vyjádření etické komise UK FTVS

k projektu diplomové práce, zahrnující lidské účastníky

Název: The Analysis Of The Effect Of Hbot In Pacients After Acute Ischemic Stroke
Forma projektu: diplomová práce

Autor/ hlavní řešitel/ Tufikameni Jason
spoluřešitelé MUDr. Jana Sůvová
Školitel (v případě studentské práce): Mgr. Michaela Prokešová

Popis projektu The purpose of this report is to give an analysis of the effectiveness of HBOT in patients after stroke. An observation of a patient was carried out before, during and after the application of hyperbaric oxygen therapy.

Zajištění bezpečnosti pro posouzení odborníky:

-

Etické aspekty výzkumu

-

Informovaný souhlas (přiložen)

V Praze dne 28. 03. 2008 Podpis autora .....

Vyjádření etické komise UK FTVS

Složení komise: doc.MUDr.Staša Bartůňková, CSc
Prof.Ing.Václav Bunc, CSc.
Prof.PhDr. Pavel Slepička, DrSc
Doc.MUDr.Jan Heller, CSc.

Projekt práce byl schválen Etickou komisí UK FTVS pod jednacím číslem: 0107/2008

dne: 9. 4. 2008

Etická komise UK FTVS zhodnotila předložený projekt a **neshledala žádné rozpory** s platnými zásadami, předpisy a mezinárodní směrnicemi pro provádění biomedicinského výzkumu, zahrnujícího lidské účastníky.

Řešitel projektu splnil podmínky nutné k získání souhlasu etické komise.

.....
podpis předsedy EK

razítko školy

Příloha

Informovaného souhlasu subjektu klinických zkoušek

Název zdravotnického prostředku: Nemocnice Kladno

Jméno subjektu: F. Chvojka
Datum narození: 1940
Zkoušející: Tufikameni Jason

1. Já, níže podepsaný (á) souhlasím s mou účastí na zkouškách. Je mi více než 18 let.
2. Byl (a) jsem podrobně informován (a) o cílu zkoušek, o jejich postupech, a o tom, co se ode mě očekává. Lékař pověřený prováděním zkoušek mi vysvětlil případné problémy, které by se mohly vyskytnout během mé účasti ve studii a vysvětlil mi způsoby jakými budou případná zdravotní rizika řešena.
3. Informoval (a) jsem lékaře pověřeného prováděním zkoušek o všech lécích, které jsem užíval(a) v posledních 28 dnech, i o těch, které v současnosti užívám. Bude-li mi nějaký lék předepsán jiným lékařem, budu ho informovat o své účasti v klinické studii a bez souhlasu lékaře pověřeného touto studií ho nevezmu.
4. Budu při své léčbě se svým lékařem spolupracovat a v případě výskytu jakéhokoliv neobvyklého nebo nečekaného příznaku ho budu ihned informovat.
5. Porozuměl (a) jsem tomu, že svou účast na zkouškách mohu kdykoliv přerušit, nebo odstoupit aniž by to jakkoliv ovlivnilo mou další léčbu.
6. Při zařazení do zkoušek budou moje osobní data uchována s plnou ochranou důvěrnosti dle platných zákonů ČR. Do mé původní zdravotní dokumentace budou moci na základě mého uděleného souhlasu nahlédnout za účelem ověření získaných údajů zástupci sponzora, nezávislých etických komisí a zahraničních nebo místních kompetentních úřadů (v ČR Státní ústav pro kontrolu léčiv). Pro tyto případy je zaručena ochrana důvěrnosti mých osobních dat. Při vlastním provádění zkoušek mohou být osobní údaje poskytnuty jiným než výše uvedeným subjektům pouze bez identifikačních údajů, to je anonymní data pod číselným kódem. Rovněž pro výzkumné a vědecké účely mohou být moje osobní údaje poskytnuty pouze bez identifikačních údajů (anonymní data) nebo s mým výslovným souhlasem.
7. Porozuměl jsem tomu, že mé jméno se nebude nikdy vyskytovat ve zprávách o těchto zkouškách. Já pak naopak nebudu proti použití výsledků těchto zkoušek.

Pacient obdržel nezbytné informace, adekvátně je pochopil a po vlastním zvážení dospěl k rozhodnutí o své účasti v projektu.

Podpis pacienta: [signature]

Datum: 08. 08. 2007

Podpis terapeutka provádějícího zkoušky: [signature]

Datum: 08. 08. 2007

Comparison of Types of Hyperbaric Oxygen Therapy Chambers

	Advantages	**Disadvantages**
Monoplaced chambers	Relatively low purchase price Requires little space and relatively minor facility renovations Modest program capitalization Treatment protocol specific to patient and/or condition Modest staffing requirements Patient does not wear mask/hood/head tent for oxygen delivery Relatively mobile chamber for possible relocation No risk of iatrogenic decompression sickness in patient or staff Add-on capability for ease of program expansion	Patient isolated during treatment Inability to suction patient Limited pressure capability (3 ATA*) Pure oxygen environment; associated fire hazard Inability to use certain diagnostic and/or therapeutic equipment (transcutaneous oxygen assessment now available [radiometer - transcutaneous monitor -3]) Increased risk of complications from pneumothorax and/or tension pneumothorax and arterial air embolism developing during decompression
Multiplaced chambers	Greater working pressure Constant patient attendance Ability to use a variety of electrically generated	Higher capitalization requirements Major space requirements; basement and/or ground floor level limitations

	signals during therapy Attendants able to enter and exit during therapy Ability to manage complications such as pneumothorax without releasing pressure Ability to conduct intensive care activities during treatment	Higher operating costs Larger and experienced staffing requirements Risk of decompression sickness in internal personnel All patients on same protocol Uncertain oxygen delivery tension at patient with face mask Severe maxillofacial and/or head and neck involvement possibly making effective delivery of oxygen difficult Facility fire-associated decompression requirements Significant equipment, maintenance and system upkeep requirements

TABLE 4 COMPERISON OF HBOT CHAMBERS (D.STEENBLOCK, 1998)

*ATA = atmosphere absolute

Primary Effects of Hyperbaric Oxygen

Mechanism	Effect	Clinical Utility
Hyperoxygenation	Greater oxygen carrying capacity Increased oxygen diffusion in tissue fluid Diffusion distance proportional	Severe blood loss anemia (unable to carry oxygen) Crush injury, compartment syndrome graft, and flap salvage

	to the square root of dissolved oxygen	(decreased perfusion) Edema (increased diffusion barrier)
Decrease gas bubble size	Boyle law - Gas volume inversely proportional to pressure Hyperbaric diffusion gradient favors gas leaving the bubble and oxygen moving in, metabolizing oxygen in the bubble Law of La Place p-4t/r Bubbles unstable as they decrease in size	Decompression sickness Air embolus syndrome

TABLE 5 Primary Effects of Hyperbaric Oxygen (JAIN KK, 1990)

Secondary Effects of Hyperbaric Medicine

Mechanism	Effect	Clinical Application
Vasoconstriction	Decreased inflow into tissues Decreased edema	Crush injuries Acute burns Compartment syndrome
Angiogenesis	Increased oxygen gradient between wound and surrounding environment	Graft and flap salvage Osteoradionecrosis

	Increased fibroblast proliferation leading to increased collagen deposition and increased fibronectin, which aids in neovascularization	Radiation endarteritis obliterans Chronic wounds
Fibroblast proliferation	Oxygen-dependent proliferation	Chronic wounds Radiation-induced injury
Leukocyte oxidative killing	Increased oxygen free radicals Anaerobes lack superoxide dismutase to control oxygen free radicals	Necrotizing soft-tissue infections Chronic osteomyelitis
Toxin inhibition	Decreased clostridial alpha toxins	Clostridial gas gangrene Decreased cardio toxins
Antibiotic synergy	Fluoroquinolones, amphotericin B, and aminoglycosides - Use oxygen to transport across cell membranes	Sepsis Necrotizing infections

Table 6 Secondary Effects Of Hyperbaric Medicine (JAIN KK, 1990)

Signs and Symptoms of Oxygen Toxicity

CNS	Pulmonary
Nausea and vomiting	Dry cough
Seizures	Substernal chest pain
Sweating	Bronchitis
Pallor	Shortness of breath
Muscle twitching	Pulmonary edema
Anxiety and/or respiratory changes	Pulmonary fibrosis
Visual changes	
Tinnitus	
Hallucinations	
Vertigo	
Hiccups	
Decreased level of consciousness	

Table 7 Signs And Symptoms Of Oxygen Toxicity (JAIN K, 1999)

Dosage	Indications
2.0 ATA* oxygen X 90 min	Wound healing Compromised skin grafts and/or flaps Thermal burns Osteomyelitis Crush injury and/or compartment syndrome Mucormycosis
2.0 ATA oxygen X 90 min with 10 min air break (high seizure risk)	Wound healing Compromised skin graft and/or flaps Thermal burns Osteomyelitis Crush injury and/or compartment syndrome Mucormycosis
2.5 ATA oxygen X 90 min	Nonclostridial gas gangrene Necrotizing infections Osteomyelitis (*Escherichia coli* or *Pseudomonas* species isolated) Late radiation tissue injury (osteoradionecrosis, soft tissue radionecrosis)
3.0 ATA oxygen X 90 min	Carbon monoxide poisoning Clostridial gas gangrene

TABLE 8 TREATMENT PROTOCOL GUIDELINES (JAIN K, 1999)

*ATA = atmosphere absolute

	Good	Bad
Microglia	Growth and trophic factors production (e.g. transforming growth factor B-1) Oxygen free radical scavenging Phagocytosis of dead cells/debris Attraction of astrocytes involved in repair processes Degradation of extracellular matrix during remodeling	Production of pro-inflammatory mediators and cytotoxins (e.g. interleukin -1B, matrix metalloproteinases) Disruption of the blood-brain barrier

Table 9 Janus/Faced Contribution Of Glieal Cells To Stroke Pathophysiology (DIRNAGL U, SIMON RP, HALLENBECK JM , 2003)